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REACTION OF ADENINE NUCLEOSIDES, TOSYLATED IN THE CARBOHYDRATE MOIETY, WITH LITHIUM TRIETHYLBOROHYDRIDE

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Abstract

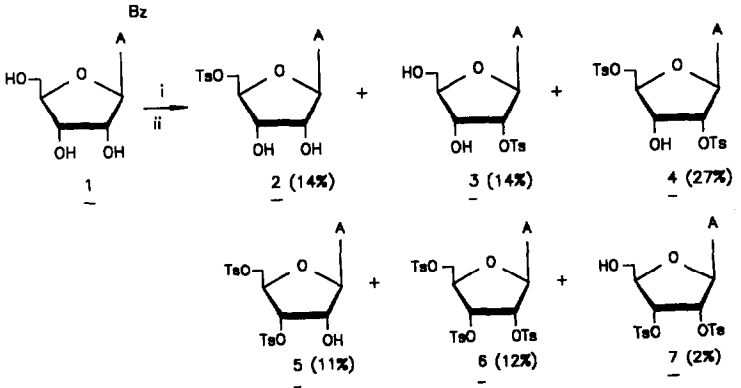
The reaction of lithium triethylborohydride with the 2',3'-di-O-p-tolylsulphonyl derivatives of 9-β-D-ribofuranosyladenine, 9-β-D-arabinofuranosyladenine, 9-β-D-xylofuranosyladenine and 9-β-D-lyxofuranosyladenine was studied. The reaction of 2',3'-di-O-p-tolylsulphonyladenosine with $LiEt_3BH$ gave 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine. This rearrangement reaction was used for the synthesis of 9-(3,5-dideoxy-β-D-threo-pentofuranosyl)adenine in one step from 2',3',5'-tri-O-p-tolylsulphonyladenosine in 58% yield.

The p-tolylsulphonyl group in the 2'-"up" configuration of unprotected adenine nucleosides was preferentially attacked by $LiEt_3BH$ giving S-O-bond scission. This was shown by the formation of 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine from 2',3'-di-O-p-tolylsulphonyl-9-β-D-arabinofuranosyladenine and by the formation of 9-β-D-lyxofuranosyladenine from 2'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine with $LiEt_3BH$. 9-β-D-Lyxofuranosyladenine was synthesized from 3',5'-di-O-benzoyl-9-β-D-xylofuranosyladenosine in 88% yield using a triflate displacement reaction.

It is not always easy to discriminate between the 2'-hydroxyl group and 3'-hydroxyl group of nucleosides during derivatization reactions. Usually a mixture of compounds are formed which are difficult to separate. This is also one of the problems for the synthesis of large amounts of nucleotide building blocks for RNA synthesis. Therefore we synthesized the 2',3'-di-O-p-tolylsulphonyl derivatives of 9-β-D-ribofuranosyladenine, 9-β-D-xylofuranosyladenine, 9-β-D-arabinofuranosyladenine and 9-β-D-lyxofuranosyladenine and studied their behaviour in the presence of $LiEt_3BH$. Lithium triethylborohydride ($LiEt_3BH$) is a powerful reducing agent for alkyltosylates[1,2]. $LiEt_3BH$ also cleaves epoxides very readily[3,4] and reduces ketones to secondary alcohols[5]. From alcohols, $LiEt_3BH$ abstracts protons with the formation of lithium salts which coordinate with triethylborane[5]. These reactions were observed when adenine nucleosides, tosylated in the carbohydrate moiety, were treated with $LiEt_3BH$. The original aim, at the start of these studies, was to find a method for the synthesis of 9-(3,5-dideoxy-β-D-threo-pentofuranosyl)adenine from easily attainable starting material.

The compounds obtained, when N^6-benzoyladenosine (1) is treated with an excess of p-tolylsulphonyl chloride (10 equivalents) in pyridine at room temperature overnight, are depicted in scheme 1. It is interesting to mention that 2'-O-p-tolylsulphonyladenosine was obtained in the same quantity as 5'-O-p-tolylsulphonyladenosine although the 2'-hydroxyl group is a secondary alcohol. This, once again, shows the influence of the acidity of a cis-diol function in derivatization reactions. T.L.C. analysis on silica ($CHCl_3$-MeOH 90:10) shows 5'-O-p-tolylsulphonyladenosine (2) as the most polar compound among mono-tosylated adenosines. This is easily explained by the presence of a cis-vicinal diol function which

is not present in 2'-O- or 3'-O-p-tolylsulphonyladenosine. On the other hand, 2',3'-di-O-p-tolylsulphonyladenosine (7) has the highest mobility on T.L.C. among the di-tosylated compounds. A larger amount of 2',3'-di-O-p-tolylsulphonyladenosine (7) was synthesized from N^6,5'-O-dibenzoyladenosine[6].



SCHEME 1

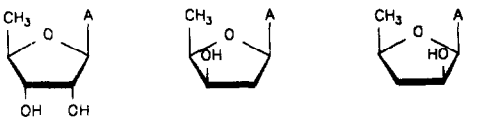
i:TsCl,pyridine ii:NH_3,MeOH

A:adenine Ts: p-tolylsulphonyl Bz:benzoyl

The rapid reduction of p-tolylsulphonates by lithium triethylborohydride ($LiEt_3BH$) is shown by the conversion of 5'-O-p-tolylsulphonyladenosine (2) into 5'-deoxyadenosine (8) in high yield.

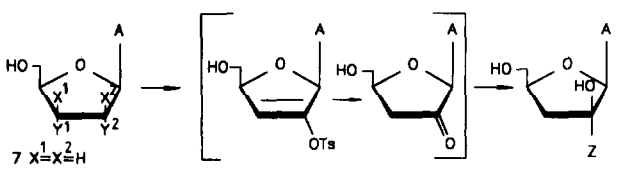
An interesting rearrangement of 2'- or 3'-mono-tosylated adenosine is described by F. Hansske and M.J. Robins[7]. When these compounds were treated with $LiEt_3BH$ in tetrahydrofuran with or without dimethylsulphoxide, a [1,2]-hydride shift rearrangement occurred followed by a stereoselective reduction of the keto-intermediate by excess $LiEt_3BH$. This reaction is a high yield, one step synthesis of 9-(2-deoxy-β-D-threo-pentofuranosyl)adenine and 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine.

This conversion and the reduction of the 5'-p-tolylsulphonate ester can be done simultaneously, although in moderate yield. Reaction of 2',5'-di-O-p-tolylsulphonyladenosine (4) with an excess of $LiEt_3BH$ in tetrahydrofuran at room temperature overnight gave 30% of 9-(2,5-dideoxy-β-D-threo-pentofuranosyl)adenine (9). Reaction of 3',5'-di-O-p-tolylsulphonyladenosine (5) in the same circumstances gave 43% of 9-(3,5-dideoxy-β-D-threo-pentofuranosyl)-adenine (10) together with a second compound which was identified as 5'-deoxyadenosine (8) (12% yield). This compound (8) results from direct attack of the hydride at sulfur with recovery of the alcohol[1]. This side reaction was not observed with 4.



The preparation of 2'-O-p-tolylsulphonyladenosine (3) is an easy reaction when a 2',3'-O-stannylene function is used for the activation of the cis-diol group[8]. However, 3'-O-p-tolylsulphonyladenosine, which gives access to 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine is more difficult to synthesize[9]. 2',3'-Di-O-p-tolylsulphonyl nucleosides are easy to prepare.

When 2',3'-di-O-p-tolylsulphonyladenosine (7) was treated with $LiEt_3BH$ at room temperature overnight, 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine (11a) was formed in 40% yield. The formation of this compound can be explained via an elimination reaction to give the intermediate 9-(3-deoxy-2-O-tosyl-β-D-glycero-pent-2-enofuranosyl)adenine which is further detosylated to 9-(3-deoxy-β-D-glycero-pentofuran-2-ulosyl)adenine and reduced from the α-face by excess reagent (scheme 2). When the reaction was repeated with lithium triethylborodeuteride ($LiEt_3BD$), 9-(3-deoxy-2-deuterio-β-D-threo-pentofuranosyl)adenine (11b) was formed. This proves that the compound is indeed formed via the stereoselective reduction of a 3'-deoxy-2'-ketoadenosine intermediate[10]. Further support is given by the ease with which 2',3'-di-O-p-tolylsulphonylated nucleosides undergo elimination reaction by proton abstraction in the 2'-position[11,12]. An analogue rearrangement was described with magnesium methoxide-sodium borohydride on N^6,5'-O-di(dimethoxytrityl)-3'-O-methylsulphonyl-2'-O-p-tolylsulphonyladenosine[13].



SCHEME 2

As could be expected, the reaction of 2',3',5'-tri-O-p-tolylsulphonyladenosine (6) with $LiEt_3BH$ gave 9-(3,5-dideoxy-β-D-threo-pentofuranosyl)adenine (10) in 58% yield. This reaction is of considerable value for the synthesis of this compound (10) because of the easy accessibility of the starting material. Starting with N^6-benzoyladenosine (1) only three steps are needed for the preparation of this, otherwise synthetically difficult nucleoside.

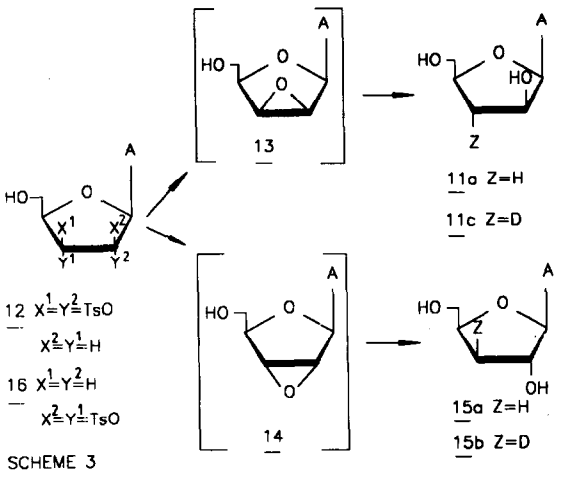
The products which are formed during reactions with carbohydrates change by introduction of protecting groups. For example, the reaction of 5'-O-monomethoxytrityl-2',3'-di-O-p-tolylsulphonyladenosine gave the expected 9-(3-deoxy-5-O-monomethoxytrityl-β-D-threo-pentofuranosyl)adenine in 53% yield together with 12% of 5'-O-monomethoxytrityladenosine. The latter, resulting from attack on sulfur, was not observed in the reaction with 2',3'-di-O-p-tolylsulphonyladenosine (7). The somewhat higher yields in this reaction could also be due to a more easy work up procedure when the 5'-hydroxylgroup is protected.

Table I : Synthesis of 2',3'-di-O-p-tolylsulphonylated adenine nucleosides

Starting material	reaction conditions (p-tolylsulphonyl chloride in pyridine)	deprotection	compound mp	yield
N^6,5'-O-dibenzoyladenosine	20 equiv. 16 h. RT	NH_3 MeOH RT 16 h.	7 207-208°C	26%
N^6,5'-O-di(triphenylmethyl)-9-β-D-xylofuranosyladenine	20 equiv. 2 days RT	HOAc 80% 80°C 45 min	12 198-199.5°C	81%
N^6,5'-O-di(monomethoxytrityl)-9-β-D-arabinofuranosyladenine	40 equiv. 4 days RT	HOAc 80% 60°C 1h	16 206-207°C	42%
N^6,5'-O-di(monomethoxytrityl)-9-β-D-lyxofuranosyladenine	40 equiv. 1 week RT	HOAc 80% 60°C 1h	17 228-229°C	39%

Reaction of 2',3'-Di-O-p-tolylsulphonyl-9-β-D-xylofuranosyladenine (12) with $LiEt_3BH$ gave two compounds which were identified as 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine 11a (10%) and 9-(3-deoxy-β-D-erythro-pentofuranosyl)adenine 15a (36%). A different reaction mechanism can be assumed in the the formation of these compounds. However, it is clear from the reaction with $LiEt_3BD$, giving 9-(3-deoxy-3-(S)-deuterio-β-D-threo-pentofuranosyl)adenine (11c) and 9-(3-deoxy-3-(R)-deuterio-β-D-erythro-pentofuranosyl)adenine (15b), that these nucleosides are formed via the formation of 2',3'-anhydro-9-β-D-lyxofuranosyladenine 13 and 2',3'-anhydroadenosine 14, respectively. The correct configuration of the deuteriated compounds is proven by the unambiguous synthesis of 11c and 15b from the anhydro compounds 13 and 14 with $LiEt_3BD$[15]. 9-(3-Deoxy-3-(S)-deuterio-β-D-threo-pentofuranosyl)adenine (11c) was synthesized in a one pot reaction starting from 9-β-D-arabinofuranosyladenine, using Mitsunobu conditions for epoxidation[16]. Epoxide formation from trans di-O-sulphonates has also been shown in the conversion of 7-(5'-O-trityl-2',3'-di-O-mesyl-α-D-arabinofuranosyl)hypoxanthine to 5'-O-trityl-3',6-anhydro-7-α-D-arabinofuranosylhypoxanthine with sodium ethanolate in ethanol[17] and in the conversion of 7-(5'-O-trityl-2',3'-di-O-p-tolylsulphonyl-β-D-xylofuranosyl)theophylline in 5'-O-trityl-2',3'-anhydro-7-β-D-ribofuranosyltheophylline with sodium methoxide in methanol-chloroform[18].

5'-O-Tritylation can prevent, to a great extent, attack of $LiEt_3BH$ on the 3'-O-tosyl-group. The reaction of 5'-O-trityl-2',3'-di-O-p-tolylsulphonyl-9-β-D-xylofuranosyladenine with $LiEt_3BH$ gave 9-(3-deoxy-5-O-trityl-β-D-erythro-pentofuranosyl)adenine (5'-O-tritylcordycepin) in 46% with only traces of the 2'-epimer.



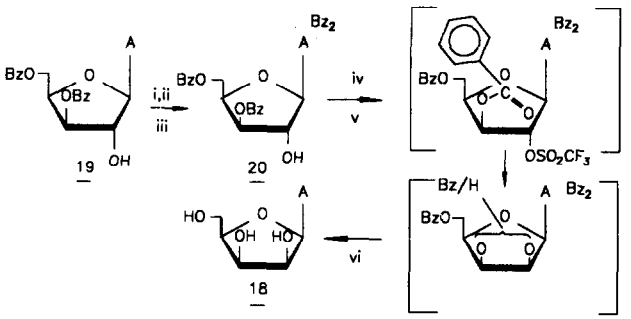
SCHEME 3

Reaction of 2',3'-di-O-p-tolylsulphonyl-9-β-D-arabinofuranosyladenine (16) with $LiEt_3BH$ did not give the same compound mixture as with the 9-β-D-xylofuranosyladenine analogue. Only one compound was formed, isolated in 85% yield, and identified as 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine (11a). The reaction with $LiEt_3BD$ gave 9-(3-deoxy-3-(S)-deuterio-β-D-threo-pentofuranosyl)adenine (11c). No incorporation of deuterium in the 2'-position was observed. Because of the (S)-configuration of the 3'-carbon atom, a direct nucleophilic displacement of the 3'-O-tosylgroup of 16 with the powerful nucleophilic $LiEt_3BD$ is excluded. This demonstrates that 11a is formed via complexation of $LiEt_3BH$ at the most hindered β-face with formation of 2',3'-anhydro-9-β-D-lyxofuranosyladenine (13) as intermediate. Recently, Matsuda et al[19] described the reaction of a Grignard reagent (MeMgBr) with a 2'-ketonucleoside, alkylated in the 4-position. Here too, the reagent approaches from the more hindered β-face. However, the observed stereoselectivity was less (4:5).

For the study of 2',3'-di-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (17) we required a synthesis of 9-β-D-lyxofuranosyladenine (18) which is more straightforward and gives less side compounds than those described in literature[20,21].

3',5'-Di-O-benzoyl-9-β-D-xylofuranosyladenine (19) is easily available from adenine and 1,2-di-O-acetyl-3,5-di-O-benzoyl-D-xylofuranose[22]. This compound was used as starting material for the synthesis of 9-β-D-lyxofuranosyladenine (18). First the adenine base was protected with benzoyl groups using the trimethylsilyl group for the transient protection[23] of the 2'-hydroxyl group. This trimethylsilyl group can be easily removed by simple addition of H_2O to the reaction mixture. In this way, N^6,N^6, 3'-O,5'-O-tetrabenzoyl-9-β-D-xylofuranosyladenine (20) was obtained in 80% yield from 19. The reaction mixture also contains some N^6-mono-benzoylated analogue. The inversion of the configuration in the 2'-position was carried out with assistance of the 3'-O-benzoyl protecting group and with use of trifluoromethanesulphonic anhydride for the activation of the 2'-hydroxylgroup (scheme 4). This reaction gives a mixture of the 2'-O-benzoyl- and 3'-O-benzoyl derivative with one and two benzoyl groups on the base moiety. It is therefore decided to debenzoylate the whole

reaction mixture and isolate directly 9-β-D-lyxofuranosyladenine (18). The one pot synthesis of 9-β-D-lyxofuranosyladenine (18) from 3',5'-di-O-benzoyl-9-β-D-xylofuranosyladenine (19), as shown in scheme 4, was carried out in a yield of 88%. Because of the high reactivity of the triflate leaving group, no nucleoside with an arabinofuranosyl or a xylofuranosyl configuration was formed. This is in contrast with the results of E. Reist et al., using a 2'-O-methylsulphonyl group[20]. 9-β-D-Lyxofuranosyladenine is the most polar compound of all four adenine nucleosides.



SCHEME 4

i: trimethylsilyl chloride, pyridine
ii: benzoyl chloride, pyridine iii: H_2O
iv: $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2
v: H_2O, 40 C· vi: NH_3, MeOH·

Reaction of 9-β-D-lyxofuranosyladenine with 3 equivalents of monomethoxytrityl chloride in pyridine gave N^6,5'-O-di(monomethoxytrityl)-9-β-D-lyxofuranosyladenine in 81% yield. This compound was tosylated with 40 equivalents of p-tolylsulphonyl chloride in pyridine for 1 week and detritylated with 80% of aqueous acetic acid. TLC analysis ($CHCl_3$-MeOH 90:10) shows two spots. The most apolar compound was isolated in 39% yield and identified as 2',3'-di-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (17). The other material proved to be a mixture of 3'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (21) and 2'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (22). Separation of both compounds could be performed on silica with Et_2O-MeOH-Et_3N (78:20:2) as eluent and on reversed phase (C-2) with MeOH-H_2O (50:50) as eluent.

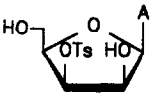
Treatment of 2',3'-di-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (17) with $LiEt_3BH$ afforded 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine (11a) in 68% yield. The position of deuterium in the 2'-position of 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine (11b) by reaction with $LiEt_3BD$ suggest the same reaction mechanism as proposed for the compound with the ribo configuration. Elimination reaction from 2',3'-di-O-sulphonylated pyrimidine nucleosides with the lyxofuranosyl configuration has been observed in the past[24,25].

Table II : Products obtained by reaction with $LiEt_3BH$ in THF at room temperature for 16 h

Substrate	Products (yield)
2	8 (86%)
4	9 (30%)
5	10 (43%) + 8 (12%)
6	10 (58%)
7	11a (40%)
7*	11a* (53%) + adenosine* (12%)
12	15a (36%) + 11a (10%)
12*	15a* (46%) + 11a* (traces)
16	11a (85%)
17	11a (68%)
21	11a (70%)
22	18 (52%)

*5'-hydroxylgroup protected with a trityl (12) or monomethoxytrityl (7) group

Finally, we were interested if the deoxygenative [1,2]-hydride shift rearrangement, described by F. Hansske and M.J. Robins[7], also takes place with 2'- or 3'-mono-tosylated 9-β-D-lyxofuranosyladenine. When 3'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine was treated with $LiEt_3BH$, 70% of 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine (11a) was isolated. The intermediate formation of 3'-deoxy-2'-ketoadenosine was proven by the reaction with $LiEt_3BD$ which gave 9-(3-deoxy-2-deuterio-β-D-threo-pentofuranosyl)adenine (11b), exclusively. This indicates the same reaction mechanism as proposed for 3'-O-p-tolylsulphonyl-adenosine[7] and that no direct attack of the hydride on the 3'-position occured. The reaction is, however, different with 2'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine. Reaction of 22 with $LiEt_3BH$ gave 9-β-D-lyxofuranosyladenine (18) as most important compound in 52% yield. The reaction with $LiEt_3BD$ gave, of course, no incorporation of deuterium. As mentioned earlier, this direct attack of $LiEt_3BH$ on the sulfur atom of the tosyl group in the 2'-"up" configuration was also observed with the 9-β-D-arabinofuranosyl analogue 16.



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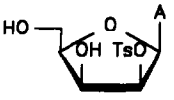

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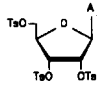
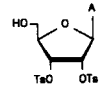
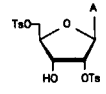
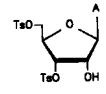
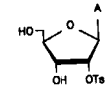
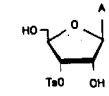
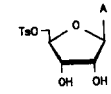
Experimental section

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with a Philips PU 8740 spectrophotometer. Mass spectra were determined with an AEI MS-12 apparatus. The ^1H NMR spectra were determined with a JEOL FX90Q spectrometer with tetramethylsilane as internal standard (s = singlet; d = doublet; t = triplet; br = broad signal; m = multiplet). Precoated Merck silica gel F254 plates were used for TLC, and the spots were examined with UV light and sul-

Table III : ^{1}H NMR data for tosylated adenosine[a,b]

	H-1'	$J_{1',2'}$	H-2'	H-3'	H-4'	H-5'	CH_3	NH_2	OH
	5.93	5.3	5.53	5.33	4.41	4.16	2.30, 2.38, 2.44	6.21	-
	6.21	7.7	5.70	5.24	4.25	3.60	2.27, 2.45	7.50	5.98
	6.02	6.2	5.57	- 4.0 -	4.25 -		2.28, 2.38	7.35	6.15
	5.86	5.3	4.93	5.25	- 4.08 -	4.48 -	2.37, 2.42	7.32	6.12
	6.10	7.2	5.48	4.35	4.05	3.56	2.29	7.36	5.70, 6.0
	5.97	5.7	- 4.76 -	5.08 -	4.08	3.50	2.43	7.38	5.88, 5.60
	5.87	5.3	4.63	- 3.98 -	4.37 -		2.37	7.30	5.39, 5.57

[a] All spectra were taken in DMSO-d_6 except 1,2,3-tri-O-p-tolylsulphonyladenosine which was taken in $CDCl_3$

[b] Tetramethylsilane was used as internal standard

furic acid-anisaldehyde spray. Column chromatography was performed on silica gel (Janssen Chimica, 0.060-0.200 mm). Dichloromethane was stored for 2 days on P_2O_5 and distilled; pyridine was refluxed overnight over potassium hydroxide and distilled. 1 M lithium triethylborohydride in tetrahydrofuran was bought from Janssen Chimica.

Tosylation of N^6-benzoyladenosine

A solution of 3.2 g (12 mmol) of N^6-benzoyladenosine and 22.9 g (120 mmol) of p-tolylsulphonyl chloride in 250 mL of anhydrous pyridine was kept overnight at room temperature. After addition of 5 mL of H_2O, the reaction mixture was evaporated, diluted with $CHCl_3$ (150 mL) and washed with H_2O (2x150 mL). The organic layer was dried, evaporated and coevaporated with toluene. Column chromatographic purification (1) $CHCl_3$ 2) $CHCl_3$-MeOH 98:2) gave 1.38 g (1.66 mmol, 14%) of N^6-benzoyl-2',3',5'-tri-O-p-tolylsulphonyladenosine, 240 mg (0.35 mmol, 3%) of N^6-benzoyl-2',3'-di-O-p-tolylsulphonyladenosine, 4.07 g (6 mmol, 50%) of a mixture of N^6-benzoyl-2',5'-di-O-p-tolylsulphonyladenosine and N^6-benzoyl-3',5'-di-O-p-tolylsulphonyladenosine, and a mixture of N^6-benzoyl-2'-O-p-tolylsulphonyladenosine and N^6-benzoyl-5'-O-p-tolylsulphonyladenosine.

These compounds were completely identified after debenzoylation with ammonia in methanol at room temperature overnight. These debenzoylated compounds are easier to separate by chromatography. Preparative thin layer chromatography ($CHCl_3$-MeOH 90:10) was necessary to separate the mixed fractions of 2',5'-ditosyl- and 3',5'-ditosyladenosine.

2',3',5'-tri-O-p-tolylsulphonyladenosine (6) ($CHCl_3$-MeOH 96:4) : 1.08 g (1.48 mmol, 12.3 %) UV (MeOH) λ_{max} 262 nm (log ε4.26). Elem. anal. $C_{31}H_{31}N_5O_{10}S_3$ calculated : C 51.02 H 4.28 N 9.60 found. C 50.93 H 4.13 N 9.40.

2',3'-di-O-p-tolylsulphonyladenosine (7) ($CHCl_3$-MeOH 96:4) : 150 mg (0.26 mmol, 2.2%) : mp (MeOH) 207-208°C. (lit[11] mp : 207-209°C).

2',5'-di-O-p-tolylsulphonyladenosine (4) ($CHCl_3$-MeOH 97:3) : 1.9 g (3.3 mmol, 27.5%) : mp (MeOH) : 106°C (soften); UV (MeOH) λ_{max} 261 nm (log ε 4.26); Elem. anal. $C_{24}H_{25}N_5O_8S_2.H_2O$ calculated : C 48.56 H 4.58 N 11.80 found : C 48.87 H 4.67 N 11.78.

3',5'-di-O-p-tolylsulphonyladenosine (5) ($CHCl_3$-MeOH 97:3); 790 mg (1.38 mmol; 11.5%) : UV (MeOH) λ_{max} 261 nm (log ε 4.25). Elem. anal. $C_{24}H_{25}N_5O_8S_2$ calculated C 50.08 H 4.38 N 12.17 found C 50.03 H 4.28 N 11.98.

2'-O-p-tolylsulphonyladenosine (3) ($CHCl_3$-MeOH 96:4) : 700 mg (1.67 mmol, 13.8%) : mp. 228-229°C (lit.[8] 229-230°C; lit.[26,27] 222-223°C).

5'-O-p-tolylsulphonyladenosine (2) ($CHCl_3$-MeOH 96:4) : 720 mg (1.71 mmol, 14.2%) mp. 169°C (lit[28] mp 155-156°C) UV (MeOH) λ_{max} 261 (log ε4.20).

Tosylation of N^6,5'-O-dibenzoyladenosine[6]

A solution of 3.8 g (8 mmol) of N^6,5'-O-dibenzoyladenosine[6] and 30.5 g (160 mmol) of p-tolylsulphonyl chloride in 200 mL of anhydrous pyridine was kept overnight at room temperature. After addition of H_2O, the reaction mixture was evaporated, diluted with $CHCl_3$ (250 mL) and washed twice with H_2O (2x100 mL). The organic layer was dried, evaporated and coeva-

porated with toluene. The residual yellow foam was dissolved in 150 mL of methanol, saturated with ammonia. The solution was kept at room temperature overnight, evaporated and purified by column chromatography (1) $CHCl_3$-MeOH 98:2 2) $CHCl_3$-MeOH 96:4) giving 1.21 g (2.1 mmol, 26%) of 2',3'-di-O-p-tolylsulphonyladenosine (7), 1.45 g (3.4 mmol, 43%) of 2'-O-p-tolylsulphonyladenosine (3) and 860 mg (2.0 mmol, 25%) of 3'-O-p-tolylsulphonyladenosine (9). This last compound was formed only in trace amounts when a tert-butyldimethylsilyl group was used to protect the 5'-hydroxyl group.

Reaction of 5'-O-p-tolylsulphonyladenosine (2) with $LiEt_3BH$

A solution of 250 mg (0.6 mmol) of 5'-O-p-tolylsulphonyladenosine (2) in 5 mL of a solution 1 M of lithium triethylborohydride in tetrahydrofuran was kept for 1h at room temperature. After addition of H_2O (0.5 mL), the reaction mixture was evaporated and purified by column chromatography ($CHCl_3$-MeOH 90:10) giving 130 mg (0.52 mmol, 86%) of 5'-deoxyadenosine. mp : 211°C[29] (lit[30] 210-212°C lit[31] 212-213°C). UV (MeOH) λ_{max} : 260 nm. MS m/e : 251 (M^+) ^1H NMR (DMSO-d_6) δ: 1.31(d,J = 6.0 Hz, CH_3); 3.96 (m, 2H, H-3', H-4'); 4.65 (m, H-2'); 5.10 (brd, OH); 5.38 (brd, OH); 5.85 (d, J = 4.8 Hz, H-1'); 7.22 (brs, NH_2); 8.13 (s) and 8.28 (s) (H-2 and H-8) ppm.

Reaction of 2',3',5'-tri-O-p-tolylsulphonyladenosine (6) with $LiEt_3BH$

A solution of 1.1 g (1.5 mmol) of 2',3',5'-tri-O-p-tolylsulphonyladenosine (6) in 15 mL 1 M of lithium triethylborohydride in tetrahydrofuran was kept at room temperature overnight. The excess reagent was hydrolized with H_2O (1 mL) and the mixture was evaporated and purified by column chromatography ($CHCl_3$-MeOH 90:10) giving 205 mg (0.87 mmol, 58% yield) of 9-(3,5-dideoxy-β-D-threo-pentofuranosyl)adenine. mp (aceton) : 208-209°C. (lit[32] mp : 208-210.5°C) UV (MeOH) λ_{max} : 260 nm (log ε 4.17). ^1H NMR (DMSO-d_6) δ : 1.34 (d, J = 6.2 Hz, CH_3); 1.62-1.99 (m, 1H, H-3'); 2.26-2.58 (m, 1H, H-3"); 4.10 (m, H-4'); 4.51 (m, H-2'); 5.35 (d, OH); 6.10 (d, J = 5.5 Hz, H-1'); 7.18 (brs, NH_2); 8.11 and 8.12 (s, 2H, H-2 and H-8) ppm.

Reaction of 3',5'-di-O-p-tolylsulphonyladenosine (5) with $LiEt_3BH$

A solution of 3',5'-di-O-p-tolylsulphonyladenosine (5) (575 mg, 1 mmol) in 1 M of lithium triethylborohydride (10 mL) was kept for 16 h at room temperature. H_2O (1 mL) was added, the mixture was evaporated and purified by column chromatography ($CHCl_3$-MeOH 92:8) giving 100 mg (0.43 mmol, 43%) of 9-(3,5-dideoxy-β-D-threo-pentofuranosyl)adenine and 30 mg (0.12 mmol, 12%) of 5'-deoxyadenosine.

Reaction of 2',5'-di-O-p-tolylsulphonyladenosine (4) with $LiEt_3BH$

Column chromatographic purification ($CHCl_3$-MeOH 90:10) gave 70 mg (0.30 mmol, 30%) of 9-(2,5-dideoxy-β-D-threo-pentofuranosyl)adenine. mp : 211°C. (lit[32] 212-213°C). UV (MeOH) λ_{max} : 260 nm ($\log_\varepsilon$ 4.18). ^1H NMR (DMSO-d_6) δ: 1.24 (d, CH_3); 2.10-2.36 (m, H-2'); 2.56-2.97 (m, H-2"); 4.10 (m, H-4'); 4.32 (m, H-3'); 5.88 (d, OH); 6.16 (dd, H-1'); 7.26 (brs, NH_2); 8.12 (s) and 8.27 (s) (H-2 and H-8) ppm.

Reaction of 2',3'-di-O-p-tolylsulphonyladenosine (7) with $LiEt_3BH$

Column chromatography ($CHCl_3$-MeOH 90:10) gives 100 mg (0.4 mmol, 40%) of 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine which was indistinguishable by UV, ^1H NMR and TLC from the compound synthesized by a literature procedure[7].

2',3'-di-O-p-tolylsulphonyl-9-β-D-xylofuranosyladenine (12)

A solution of 5.63 g (7.5 mmol) of N^6,5'-O-di(triphenylmethyl)-9-β-D-xylofuranosyladenine[14] and 28.5 g (150 mmol) of p-tolylsulphonyl chloride in 200 mL of anhydrous pyridine was kept at room temperature for 2 days. After addition of H_2O (10 mL), the reaction mixture was concentrated, diluted with $CHCl_3$ (250 mL) and washed twice with H_2O (2x200 mL). The organic layer was dried, evaporated and coevaporated with toluene. The residual yellow foam was dissolved in 80% of aqueous acetic acid and heated for 45 min at 80°C. The solvent was evaporated in vacuo and the oily residue was purified by column chromatography (1) $CHCl_3$-MeOH 98:2) 2) $CHCl_3$-MeOH 95:5) giving 2.52 g (3.08 mmol, 41%) of 5'-O-trityl-2',3'-di-O-p-tolylsulphonyl-9-β-D-xylofuranosyladenine : UV (MeOH) λ_{max} : 262 nm (log ε4.22); ^1H NMR (DMSO-d_6) δ : 2.27 (s, CH_3); 2.39 (s, CH_3); 2.70-3.56 (m, H-5'); 4.48 (m, H-4'); 5.60 (dd, H-3'); 5.92 (dd, H-2'); 6.10 (d, J = 5.7 Hz, H-1'); 6.82-7.60 (m, trityl, tosyl and NH_2); 7.89 (s) and 7.97 (s) (H-2 and H-8) ppm and 1.77 g (3.08 mmol, 41%) of 2',3'-di-O-p-tolylsulphonyl-9-β-D-xylofuranosyladenine which was crystallized from MeOH. mp 198-199.5°C. UV (MeOH) λ_{max} 262 nm (log ε 4.23) ^1H NMR (DMSO-d_6) δ: 2.28 (s, CH_3); 2.44 (s, CH_3); 3.60 (m, H-5'); 4.27 (m, H-4'); 5.47-5.86 (m, H-2', H-3'); 6.06 (d, J = 5.9 Hz, H-1'); 7.05 (d), 7.36 (d), 7.49 (d), 7.80 (d) (tosyl H); 7.33 (NH_2); 8.00 (s) and 8.16 (s) (H-2 and H-8) ppm. Elem. anal. $C_{24}H_{25}N_5O_8S_2$ calculated C 50.08 H 4.38 N 12.17 found : C 49.92 H 4.46 N 12.22.

Reaction of 2',3'-di-O-p-tolylsulphonyl-9-β-D-xylofuranosyladenine (12) with $LiEt_3BH$

Column chromatographic purification ($CHCl_3$-MeOH 85:15) gave two compounds which were identified as 9-(3-deoxy-β-D-erythro-pentofuranosyl)adenine (90 mg, 0.36 mmol, 36% yield) mp : 223-224°C. (lit[33] mp 224-225°C) ^1H NMR (DMSO-d_6) δ: 1.78-2.07 (m, H-3'), 2.10-2.47 (m, H-3"); 3.63 (m, H-5'); 4.36 (m, H-4'); 4.60 (m, H-2'); 5.16 (t, 5'-OH); 5.65 (m, 2'-OH); 5.88 (d, J = 2.2 Hz, H-1'); 7.27 (brs, NH_2); 8.16 (s) and 8.36 (s) (H-2 and H-8) ppm and 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine (25 mg, 0.1 mmol, 10%) which was identical by UV, ^1H NMR and TLC with the compound obtained by the reaction of 2',3'-di-O-p-tolylsulphonyladenosine with the same reagent.

Reaction of 5'-O-trityl-2',3'-di-O-p-tolylsulphonyladenine with $LiEt_3BH$

A solution of 800 mg (0.98 mmol) of 15 in 10 mL of 1 M lithium triethylborohydride in tetrahydrofuran was stirred overnight. The excess reagent was hydrolized with H_2O (1 mL) and the reaction mixture was evaporated. The residue was dissolved in $CHCl_3$ (20 mL), washed with H_2O (2x20 mL), dried and evaporated. Column chromatographic purification ($CHCl_3$-MeOH

96:4) gave 220 mg (0.45 mmol, 46%) of 9-(3-deoxy-5-O-trityl-β-D-erytro-pentofuranosyl)adenine[34]. UV (MeOH) λ_{max} : 261 nm (log ε4.21). ^{1}H NMR ($CDCl_3$) δ: 2.14 (m, H-3'); 3.39 (m, H-5'); 4.75 (m, H-2', H-4'); 6.03 (d, H-1'); 6.63 (brs, NH_2); 7.13-7.60 (m, trityl); 8.11 (s) and 8.26 (s) (H-2 and H-8) ppm.

5'-O-monomethoxytrityl-2',3'-di-O-p-tolylsulphonyladenosine

A solution of 4.6 g (8 mmol) of 2',3'-di-O-p-tolylsulphonyladenosine and 3.7 g (12 mmol) of monomethoxytrityl chloride was kept at room temperature for 24 h. Another 1.23 g (4 mmol) of monomethoxytrityl chloride was added and the mixture was evaporated after standing overnight at room temperature. The residual oil was dissolved in $CHCl_3$ (200 mL); washed with H_2O (100 mL) dried and evaporated. Column chromatographic purification ($CHCl_3$-MeOH 99:1) gave 2.3 g (3.4 mmol, 43%) of 5'-O-monomethoxytrityl-2',3'-di-O-p-tolylsulphonyladenosine and 1.5 g (1.3 mmol, 17%) of the ditritylated compound. UV (MeOH) λ_{max} 261 nm (log ε4.23). ^{1}H NMR ($CDCl_3$) δ : 2.28 (s, CH_3); 2.42 (s, CH_3); 3.15-3.60 (m, H-5'); 4.49 (m, H-4'); 5.32 (m, H-3'); 5.84 (dd, H-2'); 6.06 (d, J = 6.6 Hz, H-1'); 6.75-7.01 (m), 7.13-7.49 (m); 7.66-8.00 (m) (trityl, 2 x tosyl, H-2 and H-8) ppm.

Reaction of 5'-O-monomethoxytrityl-2',3'-di-O-p-tolylsulphonyladenosine with $LiEt_3BH$

A solution of 2.5 g (2.95 mmol) of 5'-O-monomethoxytrityl-2',3'-di-O-p-tolylsulphonyladenosine in a 25 mL of tetrahydrofuran containing lithium triethylborohydride (1 M) was kept at room temperature overnight. After addition of H_2O (1 mL) the solution was evaporated, dissolved in EtOAc (150 mL) and washed with H_2O. The organic layer was dried, evaporated and purified by column chromatography ($CHCl_3$-MeOH 95:5) giving 810 mg (1.5 mmol, 53%) of 9-(5-O-monomethoxytrityl-3-deoxy-β-D-threo-pentofuranosyl)adenine[34] : ^{1}H NMR ($CDCl_3$) δ: 1.87-2.50 (m, H-3'); 3.40 (m, H-5'); 3.74 (s, CH_3); 4.29 (m, H-4'); 4.55 (m, H-2'); 6.15 (d, H-1'); 6.37 (brs, NH_2); 6.81 (d) and 7.26 (m) (aromatic H); 8.08 (s) and 8.16 (s) (H-2 and H-8) ppm. The structure of this compound was further proven by detritylation with 80% of acetic acid giving 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine. The second compound which was eluted from the column was identified as 5'-O-monomethoxytrityladenosine : 190 mg (0.35 mmol, 12%). Also, the structure of this compound was verified after detritylation and column chromatography giving 80 mg of adenosine.

N^6,5'-O-di(monomethoxytrityl)-9-β-D-arabinofuransoyladenine

A mixture of 2.5 g (10 mmol) of 9-β-D-arabinofuranosyladenine and 9.26 g (30 mmol) of monomethoxytrityl chloride in 150 mL of pyridine was heated at 50°C overnight. The reaction mixture was concentrated, diluted with $CHCl_3$ (200 mL), washed with H_2O (2 x 200 mL), dried and evaporated. Column chromatographic purification ($CHCl_3$-MeOH 99:1) gave 4.46 g (5.5 mmol 55%) of the title compound. UV (MeOH) λ_{max} : 275 nm (log ε4.34) ^{1}H NMR ($CDCl_3$) δ: 3.44 (m, H-5'); 3.68 (s, CH_3); 3.70 (s, CH_3); 3.99 (m, H-4'); 4.18-4.25 (m, H-2', H-3'); 6.20 (d, J = 3.5 Hz, H-1'); 6.76 (m), 7.09-7.43 (m) (aromatic H); 7.88 (s) and 8.14 (s) (H-2 and H-8) ppm.

2',3'-di-O-p-tolylsulphonyl-9-β-D-arabinofuranosyladenine (16)

A solution of 2 g (2.47 mmol) of N^6,5'-O-di(monomethoxytrityl)-9-β-D-arabinofuranosyladenine (21) and 19 g (100 mmol) of p-tolylsulphonyl chloride in 150 mL of pyridine was kept at room temperature for 4 days. The reaction mixture was cooled to 0°C, H_2O (20 mL) was added and the mixture was evaporated. The residue was dissolved in $CHCl_3$ (250 mL), washed with H_2O (2 x 250 mL), dried, evaporated and coevaporated with toluene. The residual oil was dissolved in 80% of aqueous acetic acid and heated for 1 h at 60°C. After evaporation to dryness and column chromatographic purification ($CHCl_3$-MeOH 95:5), 600 mg (1.04 mmol, 42%) of 2',3'-di-O-p-tolylsulphonyl-9-β-D-arabinofuranosyladenine was obtained. The compound was crystallized from MeOH : mp : 206-207°C. UV (MeOH) λ_{max} 261 nm (log ε 4.23). ^1H NMR (DMSO-d_6) δ : 2.32 (s, CH_3); 2.43 (s, CH_3); 3.47 (m, H-5'); 4.07 (m, H-4'); 5.03 (t, OH); 5.57 (m, H-2', H-3'); 6.32 (d, J = 5.9 Hz, H-1'); 7.13-7.35 (m, aromatic H, NH_2); 7.50 (d), 7.84 (d) (aromatic H); 8.03 (s) and 8.05 (s) (H-2 and H-8) ppm. Elem. anal. $C_{24}H_{25}N_5O_8S_2$ calculated C 50.08 H 4.38 N 12.17 found C 50.08 H 4.36 N 12.01.

Reaction of 2',3'-di-O-p-tolylsulphonyl-9-β-D-arabinofuranosyladenine (16) with $LiEt_3BH$

A solution of 120 mg (0.21 mmol) of 2',3'-di-O-p-tolylsulphonyl-9-β-D-arabinofuranosyladenine (22) in 1 M of lithium triethylborohydride in tetrahydrofuran (3 mL) was kept at room temperature overnight. After addition of H_2O (0.5 mL), the reaction mixture was evaporated and purified by column chromatography ($CHCl_3$-MeOH 90:10) giving 45 mg (0.18 mmol, 85%) of 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine.

N^6,N^6,3'-O,5'-O-tetrabenzoyl-9-β-D-xylofuranosyladenine (20)

To a solution of 1.42 g (3 mmol) of 3',5'-di-O-benzoyl-9-β-D-xylofuranosyladenine[22] (19) in 20 mL of anhydrous pyridine was added 1.6 mL (12 mmol) of trimethylsilyl chloride. The reaction mixture was stirred for 20 min at room temperature and 1.75 mL (15 mmol) of benzoyl chloride was added. After stirring for 2 hours at room temperature, 5 mL of H_2O was added and the reaction mixture was further stirred for 2 hours. The solution was evaporated, dissolved in EtOAc (200 mL), washed with H_2O (200 mL), dried and evaporated. The residue was dissolved in $CHCl_3$ (100 mL), washed with 5% of sodium bicarbonate (3x100 mL) to remove benzoic acid, washed with H_2O (100 mL), dried and evaporated again. The oily residue was then purified by column chromatography giving 1.64 g (2.4 mmol, 80% yield) of the title compound. UV (MeOH) λ_{max} 275 nm (log ε 4.33). ^1H NMR ($CDCl_3$) δ: 4.72 (m, H-5'); 4.86-5.05 (m, H-2', H-4'); 5.63 (dd, H-3'); 6.16 (d, J = 2.6 Hz, H-1'); 7.20-8.0 (m, aromatic H); 8.48 (s) and 8.51 (s) (H-2 and H-8) ppm. Elem. anal. $C_{38}H_{29}N_5O_8$ calculated C 66.76 H 4.28 N 10.24 found C 66.52 H 4.12 N 9.98.

9-β-D-lyxofuranosyladenine (18)

A mixture of 9.5 g (20 mmol) of 3',5'-di-O-benzoyl-9-β-D-xylofuranosyladenine (23) and 10 mL (75 mmol) of trimethylsilyl chloride in 300 mL of anhydrous pyridine was stirred for

30 min at room temperature. To this was added 12.3 mL (105 mmol) of benzoyl chloride. The reaction mixture was stirred for 2h30 at room temperature, H_2O (20 mL) was added, and the mixture was further stirred for 2 h at room temperature and concentrated. The residue was dissolved in $CHCl_3$ (250 mL), washed with H_2O (2x250 mL), with 10% of aqueous sodium bicarbonate (4x200 mL), with H_2O (200 mL), dried, evaporated and coevaporated with toluene. The residual foam was dissolved in 100 mL of a mixture of CH_2Cl_2-pyridine (10:1) and cooled to 0°C.

A solution of 8.5 g (30 mmol) of trifluoromethanesulphonic anhydride in dichloromethane (60 mL) was added dropwise to it and the clear solution was stirred for 15 min at 0°C. After addition of H_2O (20 mL) the emulsion was stirred at 40°C overnight. The organic layer was separated, washed with H_2O (100 mL), dried, evaporated and coevaporated with toluene. Debenzoylation was performed by dissolving the oil in methanol, saturated with ammonia, overnight at room temperature. The solvent was evaporated in vacuo. The residue was diluted with H_2O (300 mL) and washed with CH_2Cl_2. The aqueous layer contains one major compound as judged by TLC. An analytical pure sample could be obtained by flash chromatography on silica with $CHCl_3$-MeOH 60:40 giving 4.73 g (17.7 mmol, 88% yield) of 9-β-D-lyxofuranosyladenine as an amorphous powder. ^1H NMR (DMSO-d_6) δ : 3.70 (m, H-5'); 3.97 (m, H-4'); 4.15 (m, H-3'); 4.54 (m, H-2'); 4.75 (t, 5'-OH); 5.43 (d, OH); 5.73 (d, OH); 6.20 (d, J = 7.0 Hz, H-1'); 7.19 (brs, NH_2); 8.13 (s) and 8.36 (s) (H-2 and H-8) ppm. Elem. anal. $C_{10}H_{13}N_5O_4$ calculated C 44.94 H 4.90 N 26.21 found C 44.73 H 4.80 N 26.02. The compound was identical on TLC with 9-β-D-lyxofuranosyladenine obtained by a previously described method[21].

N^6,5'-O-di(monomethoxytrityl)-9-β-D-lyxofuranosyladenine

A mixture of 2.67 g (10 mmol) of 9-β-D-lyxofuranosyladenine (18) and 9.3 g (30 mmol) of monomethoxytrityl chloride in 150 mL of pyridine was heated at 50°C overnight. After addition of H_2O (10 mL), the reaction mixture was concentrated, diluted with $CHCl_3$ (200 mL), washed with H_2O (2x100 mL), dried and evaporated. The title compound was purified by column chromatography (1) $CHCl_3$ 2) $CHCl_3$-MeOH 98:2) : 6.6 g (8.1 mmol, 81 % yield). UV (MeOH) λ_{max} 275 nm (logε 4.25). ^1H NMR ($CDCl_3$) δ: 3.55 (m, H-5'); 4.09 (m, H-3', H-4'); 4.49 (m, H-2'); 5.94 (d, J = 7.2 Hz, H-1'); 6.77 (m) and 7.04-7.50 (m) (aromatic H); 7.72 (s) and 7.82 (s) (H-2 and H-8) ppm.

Tosylation of N^6,5'-O-di(monomethoxytrityl)-9-β-D-lyxofuranosyladenine

A mixture of 6 g (7.4 mmol) of N^6,5'-O-di(monomethoxytrityl)-9-β-D-lyxofuranosyladenine and 57 g (300 mmol) of p-tolylsulphonyl chloride in 250 ml of pyridine was kept for 1 week at room temperature. The reaction mixture was cooled in an ice bath, H_2O (20 mL) was added and the solvent was evaporated. The residue was diluted with $CHCl_3$ (200 mL), washed with H_2O (2x100 mL), dried and evaporated. After coevaporation with toluene, detritylation was performed with 80% of aqueous acetic acid at 60°C for 1 h. The tosylated compounds were purified by column chromatography (1) $CHCl_3$-MeOH 95:5 2) $CHCl_3$-MeOH 90:10) giving 1.67 g

(2.9 mmol, 39%) of 2',3'-di-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (17) which was crystallized from MeOH : mp 228-229°C. UV (MeOH) λ_{max} : 261 nm (log ε 4.23). ^1H NMR (DMSO-d_6) δ: 2.30 (s, CH_3); 2.45 (s, CH_3); 3.41 (m, H-5'); 4.17 (m, H-4'); 4.90 (t, 5'-OH); 5.53 (dd, H-3'); 5.74 (dd, H-2'); 6.32 (d, J = 6.8 Hz, H-1'); 7.11 (d); 7.32 (d); 7.49 (d); 7.88 (d) (tosyl H); 7.77 (s) and 8.04 (s) (H-2 and H-8) ppm. Elem. anal. $C_{24}H_{25}N_5O_8S_2.H_2O$ calculated C 48.56 H 4.58 N 11.80 found C 48.83 H 4.53 N 11.56 and 1.85 g of a mixture of 2'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine and 3'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (4.39 mmol, 59%). T.L.C. analysis on silica (Et_2O-MeOH-Et_3N 78:20:2) and on reversed phase (C-2) (MeOH-H_2O 50:50) shows separation of these compounds (ratio approximately 6:4).

The compounds were separated on silica (Merck < 230 mesh) with the first eluent. The 2'-O-p-tolylsulphonyl derivative could be crystallized from MeOH. 2'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (22) : mp 119°C (soften); UV (MeOH) λ_{max} : 260 (log ε 4.26); ^1H NMR (DMSO-d_6) δ: 2.33 (s, CH_3); 3.63 (m, H-5'); 3.95 (m, H-4'); 4.25 (m, H-3'); 4.72 (t, 5'-OH); 5.52 (dd, J = 4.6 and 7.2 Hz, H-2'); 6.21 (d, J = 7.2 Hz, H-1'); 6.43 (d, 3'-OH); 7.20 (d) and 7.46 (d) (aromatic H); 7.86 (brs, NH_2); 8.06 (s) and 8.23 (s) (H-2 and H-8) ppm. Elem. anal. $C_{17}H_{19}N_5O_6S.1/2H_2O$ calculated C 47.44 H 4.68 N 16.27 found C 47.28 H 4.64 N 16.09. 3'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (21) : UV (MeOH) λ_{max} 259.5 nm (log ε 4.25). ^1H NMR (DMSO-d_6) δ : 2.43 (s, CH_3); 3.46 (m, H-5'); 4.15 (m, H-4'); 4.70 (m, H-2'); 4.99 (5'-OH); 5.31 (t, J = 4Hz, H-3'); 6.00 (d, 2'-OH); 6.31 (d, J = 6.4 Hz, H-1'); 7.22 (brs, NH_2); 7.48 (d) and 7.89 (d) (aromatic H); 7.99 (s) and 8.13 (s) (H-2 and H-8) ppm. Elem. anal. $C_{17}H_{19}N_5O_6S$ calculated C 48.45 H 4.54 N 16.62 found C 48.22 H 4.37 N 16.41.

Reaction of 2',3'-di-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (27) with $LiEt_3BH$

The reaction mixture was purified by column chromatography ($CHCl_3$-MeOH 90:10) giving 170 mg (0.68 mmol, 68% yield) of 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine.

Reaction of 2',3'-di-O-p-tolylsulphonylated derivatives of adenosine (7), 9-β-D-xylofuranosyladenine (12), 9-β-D-arabinofuranosyladenine (16) and 9-β-D-lyxofuranosyladenine (17) with $LiEt_3BD$

These reactions were carried out as described for the reactions with $LiEt_3BH$. The following compounds were isolated :

a) from 2',3'-di-O-p-tolylsulphonyladenosine (7) : 9-(3-deoxy-2-deuterio-β-D-threo-pentofuranosyl)adenine[7] ^1H NMR (DMSO-d_6) δ : 1.84-2.15 (dd, J = 8.2 and 12.7 Hz, H-3'); 2.16-2.44 (dd, J = 6.8 and 12.7 Hz, H-3"); 3.60 (m, H-5'); 4.08 (m, H-4'); 6.12 (s, H-1'); 7.20 (brs, NH_2); 8.11 (s) and 8.27 (s) (H-2 and H-8) ppm.

b) from 2',3'-di-O-p-tolylsulphonyl-9-β-D-xylofuranosyladenine (12) : 9-(3-deoxy-3-(R)-deuterio-β-D-erythro-pentofuranosyl)adenine[35] ^{1}H NMR (DMSO-d_6) δ 1.92 (dd, J = 3.1 and 6.4 Hz, H-3'); 3.60 (m, H-5'); 4.14 (m, H-4'); 4.56 (t, J = 2.6 Hz, H-2'); 5.85 (d, J = 2.4 Hz, H-1'); 7.23 (brs, NH_2); 8.12 (s) and 8.33 (s) (H-2 and H-8) ppm and 9-(3-deoxy-3-(S)-deuterio-β-D-threo-pentofuranosyl)adenine[36] ^{1}H NMR (DMSO-d_6) δ : 2.02 (t, J = 7.6 Hz, H-3') 3.64 (m, H-5'); 4.12 (m, H-4'); 4.53 (dd, J = 5.3 and 7.5 Hz, H-2'); 6.18 (d, J = 5.3 Hz, H-1'); 7.73 (brs, NH_2); 8.25 (s) and 8.42 (s) (H-2 and H-8) ppm.

c) from 2',3'-di-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (17) : 9-(3-deoxy-2-deuterio-β-D-threo-pentofuranosyl)adenine[7] ^{1}H NMR (DMSO-d_6) δ : 1.86-2.16 (dd, H-3'); 2.16-2.44 (dd, H-3"); 3.60 (m, H-5'); 4.08 (m, H-4'); 6.12 (s, H-1'); 7.27 (brs, NH_2); 8.12 (s) and 8.32 (s) (H-2 and H-8) ppm.

d) from 2',3'-di-O-p-tolylsulphonyl-9-β-D-arabinofuranosyladenine (16) : 9-(3-deoxy-3-(S)-deuterio-β-D-threo-pentofuranosyl)adenine[36] ^{1}H NMR (DMSO-d_6) δ : 1.97 (t, 7.7 Hz, H-3'); 3.61 (m, H-5'); 4.08 (m, H-4'); 4.49 (dd after D_2O exchange, J = 5.3 and 7.5 Hz, H-2'); 5.12 (5'-OH); 5.37 (2'-OH); 6.14 (d, J = 5.3 Hz, H-1'); 7.17 (brs, NH_2); 8.12 (s) and 8.27 (s) (H-2 and H-8) ppm.

Reaction of 3'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (21) with $LiEt_3BH$ and $LiEt_3BD$

This reaction was performed and worked up as described for the previous reactions. Starting with 421 mg (1 mmol) of 3'-O-p-tolylsulphonyl-β-D-lyxofuranosyladenine, 170 mg (0.68 mmol, 68%) of 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine was obtained. When the same reaction was repeated with lithium triethylborodeuteride, 9(-3-deoxy-2-deuterio-β-D-threo-pentofuranosyl)adenine was obtained in the same yield.

Reaction of 2'-O-p-tolylsulphonyl-9-β-D-lyxofuranosyladenine (22) $LiEt_3BH$ and $LiEt_3BD$

These reactions were carried out on a 1 mmol scale as described previously. After purification by column chromatography 150 mg (0.56 mmol) 86% of 9-β-D-lyxofuranosyladenine was isolated. No deuterium incorporation was noticed by reaction with $LiEt_3BD$.

Reaction of 2',3'-anhydro-9-β-D-lyxofuranosyladenine (13) with $LiEt_3BD$

500 mg (1.87 mmol) of 9-β-D-arabinofuranosyladenine was treated with 1.5 equivalents of triphenylphosphine and 1.5 equivalents of diethyl azodicarboxylate in dioxane as described by Mengel et al[16]. After 1 h at 80°C, the reaction mixture was evaporated, diluted with Et_2O (100 mL) and decanted. The washing with absolute Et_2O was repeated twice. The resulting amorphous material was suspended in 20 mL of 1 M of lithium triethylborodeuteride[15] and stirred at room temperature overnight. Water (2 mL) was added, the reaction mixture was evaporated and purified by column chromatography ($CHCl_3$-MeOH 90:10) giving 250 mg (1 mmol,

53%) of 9-(3-deoxy-3-(s)-deuterio-β-D-threo-pentofuranosyl)adenine[36]. ^1H NMR (DMSO-d_6) δ: 2.02 (t, J = 7.8 Hz, H-3'); 3.64 (m, H-5'); 4.12 (ddd, H-4'); 4.53 (dd, J = 5.5 and 7.5 Hz, H-2'); 5.56 (2xOH); 6.18 (d, J = 5.3 Hz, H-1'); 7.73 (brs, NH_2); 8.25 (s) and 8.42 (s) (H-2 and H-8) ppm.

Reaction of 2',3'-anhydroadenosine (14) with $LiEt_3BD$

This reaction was carried out as described previously for the other reaction with lithium triethylborohydride[15]. The mixture was stirred for 4 h at room temperature. Starting from 249 mg (1 mmol) of 2',3'-anhydroadenosine, 140 mg (0.56 mmol, 56%) of 9(-3-deoxy-3-(R)-deuterio-β-D-erythro-pentofuranosyl)adenine was obtained[35]. ^1H NMR (DMSO-d_6) δ: 1.96 (dd, J = 3.3 and 6.3 Hz, H-3'); 3.68 (m, H-5'); 4.41 (m, H-4'); 4.64 (m, H-2'); 5.21 (t, 5'-OH); 5.71 (d, 2'-OH); 5.93 (d, J = 2.4 Hz, H-1'); 7.32 (brs, NH_2); 8.20 (s) and 8.40 (s) (H-2 and H-8) ppm.

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