Tetrahedron Letters Vol. 21, pp 4339 - 4342
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0040-4039/80/1101-4339$02.00/0

SYNTHESIS OF 2′-END MODIFIED 2′,5′-ADENYLATE TRIMERS

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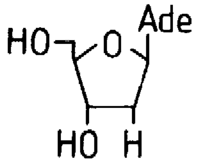
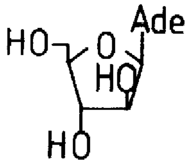
Trimeric 2′,5′-linked adenylates incorporating deoxyribosides and arabinoside of adenine in the 2′-end were synthesized by the phosphotriester approach using quinoline-8-sulfonyl nitrotriazolide as an effective condensing agent.

The rapid degradation of 2′,5′-adenylates in cell cultures by a phosphodiesterase activity[1] prompted us to synthesize 2′,5′-adenylates modified at the 2′- and 3′-end. Since it has been shown in these assays that the 2′,5′-trimeric "core" is almost as active as the triphosphate[2] we decided to concentrate on the core itself. In order to evaluate different groups in the 2′- and 3′-end of the ribose moiety we prepared adenosines 1 - 4 with modified sugars.



1



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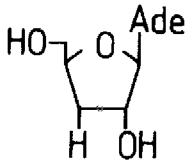

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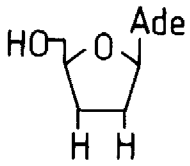
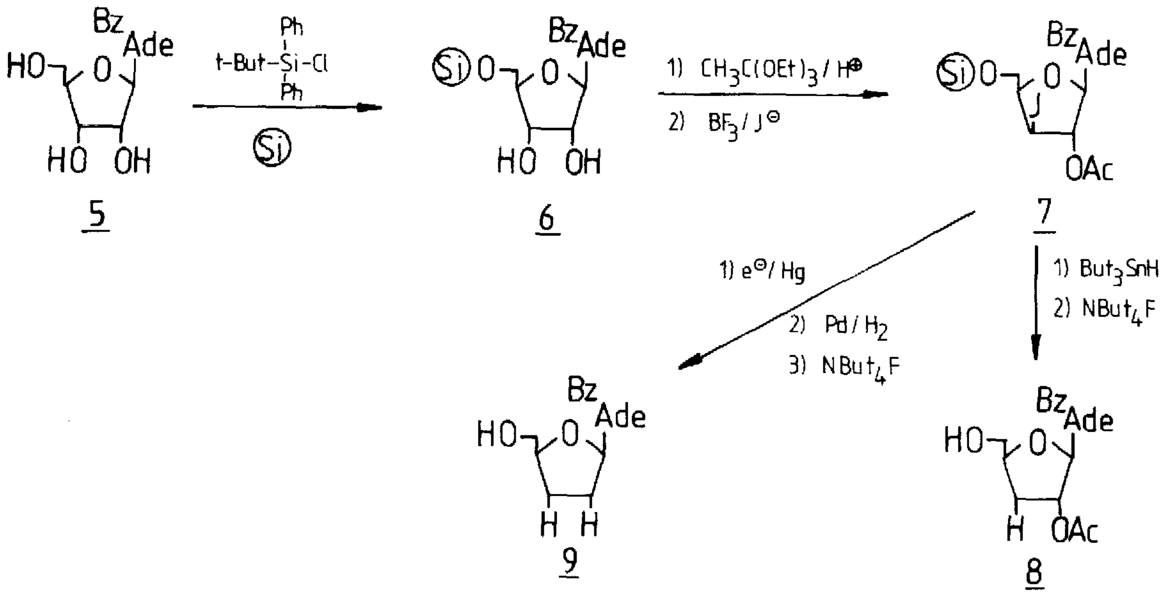


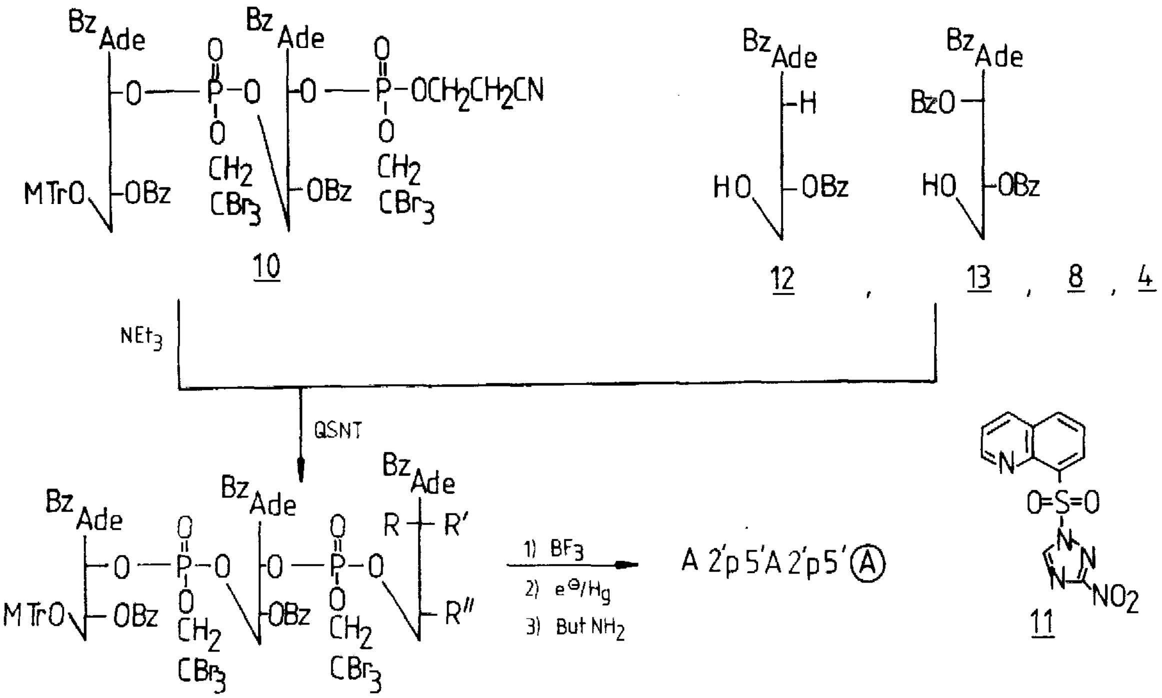
4

In the case of 2′-deoxy-A 1 and ara-A 2 the free, commercially available nucleosides were converted in the usual manner to the protected N-benzoyl, O-benzoyl-5′-hydroxyl nucleosides 12 (mp 167° C)[3] and 13 (mp 139° C) by perbenzoylation, partial debenzoylation, tritylation and again benzoylation with benzoylcyanide[4] followed by detritylation. In order to be able to attach the modified adenosine units 8, 9, 12 and 13 at the 2′-end we prepared ApAp 10 in a similar manner as outlined[5] . The properly protected 3′-deoxy compound 8 and the 2′,3′-dideoxy compound 9 were obtained by directly incorporating the desired protecting groups during synthesis from N-benzoyladenosine 5 . Conversion of 5 to the 5′-silylated 6 was effected with t-butyl-diphenylchlorosilane[6] in pyridine in 74% (mp 180°C). Reaction of 6 with triethyl orthoacetate followed by BF_3/ Et_2O and NaI in CH_3CN (0°C, 1h) gave the iodoacetyl derivative 7 in 60%. This compound can either be converted with But$_3$SnH in toluene (80°C, 1h)[7] to the 3′-deoxy derivative 8 ,which we obtained after desilylation with NBut$_4$F in THF in 76% (mp 92°C). Electrolytic reduction of the iodoacetyl derivative 7 in CH$_3$CN at the mercury pool electrode in a similar fashion as [8] resulted in the 2′,3′-unsaturated compound in 80% which can be hydrogenated on Pd/SiO$_2$ to the 2′,3′-dideoxy nucleoside 9 in 90%. Desilylation again was almost quantitative.



The nucleosides 8, 9, 12 and 13 were condensed with ApAp 10 to the ApAp Ⓐ compounds 14 - 17 with our new coupling reagent quinoline-8-sulfonyl-3-nitro-1,2,4-triazolide (QSNT) 11. This reagent was prepared from quinoline-8-sulfochloride[9] and 3-nitro-1,2,4-triazole[10] in dioxane with NEt$_3$ in 85% (mp 230°C). Not only was this the sole reagent that yielded 17 in 38% but it also compared favourably with other reagents TPSNT[11] and MSNT[12] in yielding 14 - 16 in 70 - 80% by showing similar reactivity coupled with less sulfonylation. We therefore recommend QSNT for the condensation of acid sensitive functionalities like the 2′,3′-dideoxynucleosides, which we could incorporate chemically for the first time.

The lability towards acid of the N-benzoyl- 2′,3′-dideoxy nucleoside 9 was so marked that upon detritylation most of the glycosidic bond was cleaved. In order to overcome this problem the ApAp 10 building block was first detritylated, benzoylated with benzoylcyanide and then condensed with 4, the debenzoylated 9. The final deprotection of the triesters 14 - 17 was performed by detritylation (BF_3/MeOH) followed by electrochemical deblocking (CH_3CN, Hg-pool, $NaHCO_3$ in the anolyte) of the tribromoethyl[13] moiety. The debenzoylation of the diesters was accomplished by $BuNH_2$/MeOH.



	R	R'	R''
14	H	H	OBz
15	OBz	H	OBz
16	H	OAc	H
17	H	H	H

	Ⓐ
18	1
19	2
20	3
21	4

The diesters 18 - 21 were purified on DEAE Sephadex columnswith a triethylammonium bicarbonate buffer pH = 7.5 and a linear gradient (0.1 - 0.3 M). The purity of these diesters was checked by hplc (Polygosil 60-10 $N(CH_3)_2$ from Macherey-Nagel and ammoniumformiate/CH_3CN pH = 6.2) and tlc on PEI-cellulose(NH_4HCO_3).Their characteristic ^1H-nmr data in D_2O (dioxane standard at δ = 3.71ppm) are shown in

Tab. 1

Tab. 1 NMR data of modified A2'p5'A2'p5'Ⓐ

Comp.	Adenine H2 and H8						Ribose H 1'		
18	8.11	8.07	7.97	7.95	7.90	7.76	6.07(t)	5.96(d)	5.78(d)[a]
19	8.03	7.97	7.86	7.81	7.76	7.70	6.04(d)	5.95(d)	5.92(d)
20	8.03	7.94	7.91	7.80	7.74	7.62	5.94(d)	5.85(d)	5.68(d)
21	8.03	7.96	7.92	7.88	7.77	7.65	5.99(t)	5.97(d)	5.85(d)

a) d = doublet, t = triplet

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft.

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14. All compounds have been fully characterized by spectroscopic means and elemental analyses. Significant nmr spectral data (δ, ppm from Me_4Si in $CDCl_3$) are the following: 7: 8.74, 8.35(s,H2,8), 6.23(d,H1'), 5.91(t,H2'), 4.43(m,H3'), 2.16(s,CH_3); 8: 8.70, 8.26(s,H2,8), 6.10(d,H1'), 5.60(m,H2'), 2.80(m,H3'), 2.10(s,CH_3); 9: 8.67, 8.27(s,H2,8), 6.26(t,H1'), 2.0-2.7(m,H2',2'',H3',3'')

(Received in Germany 18 June 1980)