5'-*O*-Trityl Group Promoted Directive Effect in the Preparation of 2'-*O*-Methylribonucleosides

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It has become apparent in the last decade that 2'-*O*-methylribonucleosides make a significant contribution to the structure and function of rRNA and tRNA.[1] It has also come to light in the last few years that a lack of a ribose-2'-*O*-methyl group is often responsible, in certain cases of rRNA, for the lack of formation of functional ribosomes.[1] A survey of literature[2-4] reveals several methods of partial methylation of ribonucleosides followed by extensive ion-exchange chromatographic separation and purification which eventually lead to poor overall yields of 2'-*O*-methylribonucleosides. Garegg *et al.*[5] have recently circumvented these tedious ion-exchange chromatographic separation procedures by carrying out a partial methylation on 5'-*O*-*t*-butyldiphenylsilylguanosine with the help of diazomethane in dimethylformamide at 50 °C, which is catalyzed by tin(II) chloride, followed by a facile separation of 2'- and 3'-monomethylated products by chromatography on silica gel using a chloroform–methanol mixture in the mobile phase. In this way, they obtained 5'-*O*-*t*-butyldiphenylsilyl-2'-*O*- and -3'-*O*-methylguanosine, respectively, in 22% and 40% yields. It is worthwhile emphasizing that it is the lipophilic silyl group at 5'-position that allowed these workers to resolve the 2'- and 3'-monomethyl ethers upon silica gel chromatography. We were obviously interested by their results and replaced the 5'-*O*-silyl group with a less expensive and more easily accessible trityl (triphenylmethyl-) group and repeated their experiment at 50 °C for partial methylation on 2-*N*-*t*-butylbenzoyl-5'-*O*-tritylguanosine (*1*). We isolated a glass, after a silical gel chromatography using $CHCl_3$-methanol mixture, in 48% yield. A ^1H NMR analysis of the glass showed the presence of 2'- and 3'-ethers, (*8a*) and (*10a*), respectively, in 71 and 29%. Thus the 2'-*O*-methylether of 2-*N*-*t*-butylbenzoyl-5'-*O*-tritylguanosine (*8a*) was obtained from this mixture in 29.9% yields. A more interesting observation was that when the partial methylation was carried out on (*1*) with CH_2N_2 in dimethylformamide at 0 °C and a catalytic amount of tin(II) chloride, we obtained only 2'-*O*-methyl ether (*8a*) in 43% yield. There was no detectable amount of 3'-*O*-methylether (*10a*) formed under the above condition as monitored by ^1H NMR spectroscopy. However, when we performed these partial methylations on 2-*N*-*t*-butylbenzoyl quanosine (*2*) at 0 °C and 50 °C, under the above condition we observed the formation of 2' and 3'-*O*-methyl 2-*N*-*t*-butylbenzoylquanosine, (*8b*) and (*10b*), in an almost identical ratio (55:45). The above experiments, along with Garegg and co-worker's observation, clearly lead us to attribute this hitherto unobserved phenomenon, to the trityl group at the 5'-position which is most probably exerting a directive influence on the methylation of the 2'-hydroxyl

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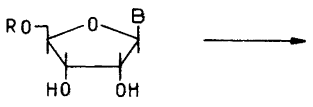
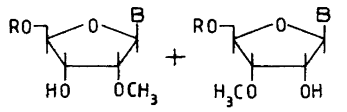


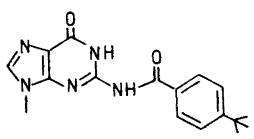
1, B=*11*, R=Tr;
2, B=*11*, R=H;
3, B=*12*, R=Tr;
4, B=*12*, R=H;

5, B=*13*, R=Tr
6, B=*13*, R=H
7, B=*14*, R=Tr
9, B=*14*, R=H



8a, B=*11*, R=Tr
8b, B=*11*, R=H

10a, B=*11*, R=Tr
10b, B=*11*, R=H



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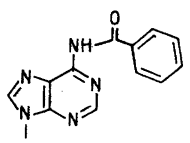

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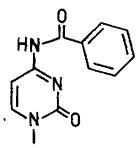

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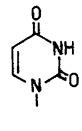

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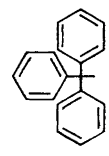

Tr (Trityl)

0302-4369/82/100715-03$02.50

Table 1. Yield and data of 2′- and 3′-methylribonucleosides.

Substrates	2′- and 3′-monomethyl ethers at 50 °C (%)[a]				2′- and 3′-methyl ethers at 0 °C (%)[a]				^{1}H NMR (δ)[b]				R_f values[c]	
	^{1}H NMR ratios		Isolated yields (%)		^{1}H NMR ratios		Isolated yields (%)		H-1′		O-CH_3			
	2′-O-CH_3	3′-O-CH_3	2′+3′	2′	2′-O-CH_3	3′-O-CH_3	2′+3′	2′	2′-	3′-	2′-	3′-	2′-	3′-
5′-O-Trityl-2-N-t-butylbenzoylguanosine (*1*)	71	29	48	29.9	100	0	43	43	5.91, 5.76		3.45, 3.41		0.45	0.44
2-N-t-Butylbenzoylguanosine (*2*)	56	44	36	–	55	45	–	–	6.01, 5.91		3.48, 3.46		0.63	
5′-O-Trityl-6-N-benzoyladenosine (*3*)	60	40	54.2	30.3	65	35	57.1	36.5	6.18, 6.0		3.52, 3.45		0.50	0.45
6-N-Benzoyladenosine (*4*)	45	55	65	–	50	50	–	–	5.95, 5.80		3,65, 3.37		0.70	
5′-O-Trityl-4-N-benzoylcytidine (*5*)	85	15	58.1	49.0	90	10	50.9	46.7	6.04, 5.95		3.76, 3.48		0.41	0.23
4-N-Benzoylcytidine (*6*)	63	37	58	–	60	40	–	–	5.94, 5.79		3.68, 3.47		0.73	
5′-O-Trityluridine (*7*)	62	38	51.6	27.6	74	26	57.6	41.2	5.96, 5.90		3.64, 3.44		0.53	0.42
Uridine (*9*)	45	55	–	–	51	49	–	–	5.87, 5.75		3.76, 3.64		0.42	

[a] These are based on 1 mmol scale experiment. [b] Solvent: $CDCl_3$ for tritylated compound and *ca.* 5% CD_3OD in $CDCl_3$ for other compounds. [c] Merck pre-coated silica gel F_{260} plates. Tritylated compounds: acetone – water – methylene chloride (30:0.5:69.5, v/v/v). Non-tritylated compounds: methanol – chloroform (20:80, v/v).

group by shielding the 3′-hydroxyl position. As far as our knowledge of the literature goes, this is the first direct evidence in ribonucleoside chemistry when a remotely located group kinetically controls the preferential formation of a product by interacting through space. Similar observations are also borne out in the case of other ribonucleoside derivatives, (*3*) to (*9*) (Table 1), when the yields of formations of 2′-*O*-methyl ethers are compared with the yield of 3′-*O*-methyl ethers, in the presence or absence of a trityl group at 5′ position, at 0 and at 50 °C.

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