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STEREOCHEMICAL CONTROL OF THE GLYCOSYLATION REACTION VIA 3,5-Di-O-(p-TOLUOYL)-2-O-(p-TOLUOLSULFONYL)-β-D-METHYL RIBOFURANOSIDE[1]

Christos PAPAGEORGIOU and Christoph TAMM*

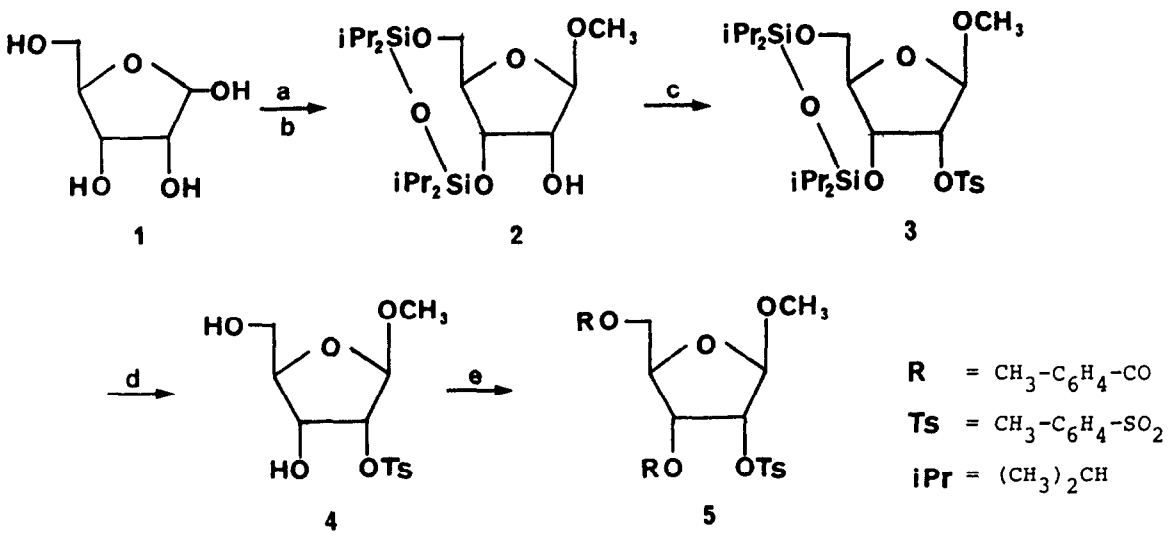
Institut für Organische Chemie der Universität
St. Johanns-Ring 19, CH-4056 Basel, Switzerland

ABSTRACT: Lewis acid catalyzed glycosylation of the 2'-tosyl ribofuranose derivative 5 leads exclusively to β-nucleosides in the uridine and adenosine series.

For our continuing studies on the chemical synthesis of oligoribonucleotides and the evaluation of their biological properties[2] it is necessary to have the monomeric nucleosidic units asymmetrically substituted. To synthesize these nucleosides, we have retained the method involving glycosylation of trimethylsilyl derivatives of nucleic bases with acylated sugar derivatives in the presence of Lewis acid[3]. The stereochemistry of the reaction is determined by the transient 1,2-acyloxonium ion[4], but recent observations indicate the possibility of stereoselective syntheses of α- or β-nucleosides starting from sugar derivatives with non-participating groups[5].

In order to investigate the feasibility of this latter route, the use of a 2'-tosyl ribufuranose derivative appeared to be reasonable because tosyl group would be bulky enough to exercise complete stereochemical control during the glycosylation step.

Scheme I outlines the synthesis of the sugar moiety 3,5-di-O-(p-toluoyl) 2-O-tosyl β-D-methyl ribofuranoside 5.



1 2 3 4 5

a) MeOH, H_2SO_4; b) $(iPr_2Si)_2O$, pyridine; c) TsCl, DAMP;
d) Bu_4NF; e) TolCl, pyridine

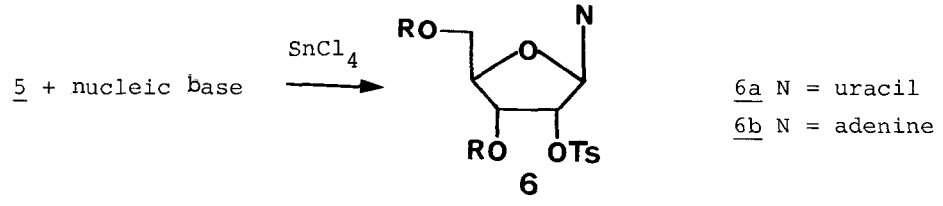
SCHEME I

For the synthesis of 5 we used 1,1,3,3-tetraisopropyl 1,3-dichlorodisilazane (TPDS-Cl_2) as a protecting group which allows the simultaneous 3,5-O-protection of ribofuranosyl compounds[6]. Thus treatment of methyl β-D-ribofuranoside[7] with the above mentioned reagent in the presence of pyridine gave the alcohol 2 in 66% yield[8]. Tosylation of the 2'-hydroxy function was effected with tosyl chloride in a solution of dimethylaminopyridine (DMAP) in acetonitrile. The ^{1}H NMR spectrum confirmed the position of the tosyl group since the H-2 resonance in 3 was observed to shift downfield by ca. 0.5 ppm from that observed in 2. Compound 3 was deprotected by a solution of tetrabutylammonium fluoride in THF to give the diol 4 in 81% yield from 2. This diol could be a versatile intermediate for synthetic studies since it is possible to distinguish between the primary and the secondary hydroxy functions[9] (tritylation, benzoylation, acylation, silylation) or obtain 2-deoxyribose derivatives. Treatment of 4 with an excess of toluoyl chloride afforded the riboside 5 in 73% yield.

All the synthetic intermediates, as well as 5, were anomerically pure and their β-assignment was established by ^{1}H NMR[10]. The anomeric H-1 appears

as a singlet in complete agreement with the general trends observed in furanose glycosides[11].

Glycosylation of 5 (SCHEME II) with silylated uracil[3] and adenine[12] in the presence of $SnCl_4$ led exclusively to the corresponding β-nucleosides: 3',5'-di-O-toluoyl 2'-tosyl uridine 6a (H-1': 6.00 ppm J=3.6Hz) and 3',5'-di-O-toluoyl 2'-tosyl adenosine 6b (H-1': 6.10 ppm J=5.0Hz) as shown by ^1H NMR analysis. Confirmation of the structure was obtained by hydrolysis (MeOH MeONa) to the known 2'-cyclouridine[13] and 2'-tosyl adenosine[6].



SCHEME II

In conclusion 2'-tosyl β-ribofuranoside 5 is an attractive compound for the direct synthesis of asymmetrically 2',3'-substituted β-ribonucleosides. Furthermore this approach represents a potentially general route to di-symmetrically substituted oligoribonucleotide building blocks.

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10) All the compounds gave HRMS and/or combustion analysis consistent with their structures.
Selected physical data:

Compound 2:

$[\alpha]_D^{25}$= -37.1° (c=3, CH_2Cl_2)

^1H NMR ($CDCl_3$): 4.81 (s, H-1); 4.51 (dd, H-3, $J_{2,3}=J_{3,4}$=5.3); 3.74-4.10 (m, H-2, H-4, H-5, H-5'); 3.33 (s, $-OCH_3$); 1.03-1.13 (m, i-Pr_4)

IR ($CHCl_3$): 3550-3400 (-OH)

Compound 3:

$[\alpha]_D^{25}$= -16.1° (c=4, CH_2Cl_2)

^1H NMR ($CDCl_3$): 7.80 (d, 2H, J=8.8); 7.29 (d, 2H, J=8.7)
4.90 (s, H-1); 4.45-4.67 (m, H-2, H-3); 3.70-4.12 (m, H-4, H-5, H-5');
3.33 (s, $-OCH_3$); 2.43 (s, $-CH_3$); 0.75-1.10 (m, i-Pr_4)

Compound 4:

$[\alpha]_D^{25}$= -8.9° (c=9, $CHCl_3$)

^1H NMR ($CDCl_3$); 7.75 (d, 2H, J=8.7); 7.37 (d, 2H, J=8.7); 4.83 (s, H-1); 4.66 (d, H-2, $J_{2,3}$=4.6); 4.20-4.50 (m, H-3, upon D_2O addition: dd, $J_{3,2}$= 4.6, $J_{3,4}$=5.7); 3.85-4.16 (m, H-4); 3.50-3.83 (m, H-5, H-5' upon D_2O addition: dd, $J_{4,5}$=4.0, $J_{4,5'}$=4.5); 3.33 (s, $-OCH_3$); 2.51 (d, -OH, J=6.7) 2.50 (s, $-CH_3$); 2.21 (m, -OH) 2.50 (s, $-CH_3$); 2.21 (m, -OH)

IR ($CHCl_3$): 3600-3400 (-OH)

Compound 5:

$[\alpha]_D^{25}$= +39.5° (c=4, CH_3Cl); m.p. 98 C

^1H NMR ($CDCl_3$): 7.0-8.0 (m, 12H); 5.45 (dd, H-3, $J_{3,2}$=4.4, $J_{3,4}$=4.8);5.10(s,H-1); 5.03 (d, H-2, $J_{2,3}$=4.4); 4.25-4.73 (m, H-4, H-5, H-5'); 3.34 (s, $-OCH_3$); 2.44 (s, $-CH_3$); 2.38 (s, $-CH_3$); 2.30 (s, $-CH_3$)

IR ($CHCl_3$): 1720 (-CO)

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