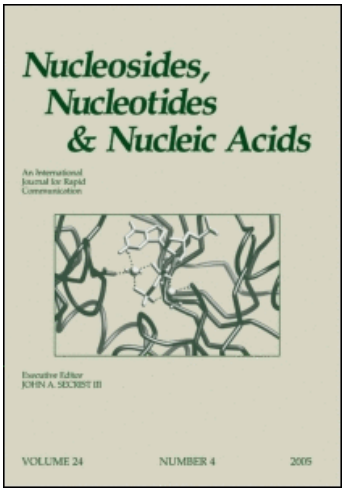

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Banuls, V. , Sarramegna, V. , Froment, C. , Escudier, J. M. and Gorrichon, L.(1999) '5'-C-Tosyloxyalkylnucleosides. Models for Oligonucleotide Coupling with Nucleophiles', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1527 — 1529
To link to this Article: DOI: 10.1080/07328319908044777
URL: http://dx.doi.org/10.1080/07328319908044777

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1527–1529 (1999)

5'-C-TOSYLOXYALKYLNUCLEOSIDES. MODELS FOR OLIGONUCLEOTIDE COUPLING WITH NUCLEOPHILES

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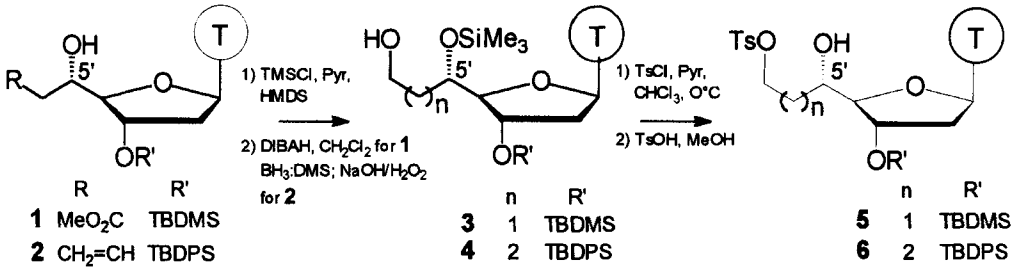
ABSTRACT: 5'-C-substituted nucleosides with an hydroxyalkyl chain are synthesized. The stereochemistry of the new stereogenic center is defined. After introduction of a tosyl group, dimer models are prepared to evaluate the conjugation with amines used as nucleophiles.

Introduction

Modification of the carbohydrate moiety of nucleosides had received important attention[1], but there is only few reports about 5'-C-substituted nucleosides.[2] This class of compounds when incorporated into oligodeoxyribonucleotides (ODN's), have a reasonable duplex stability and an increased nuclease resistance compared to non modified ODN's. An hydroxyalkyl chain placed at this position should provide an useful tool for the introduction of new functionality to ODN's, leaving the 5' and 3' ends free for other modifications.

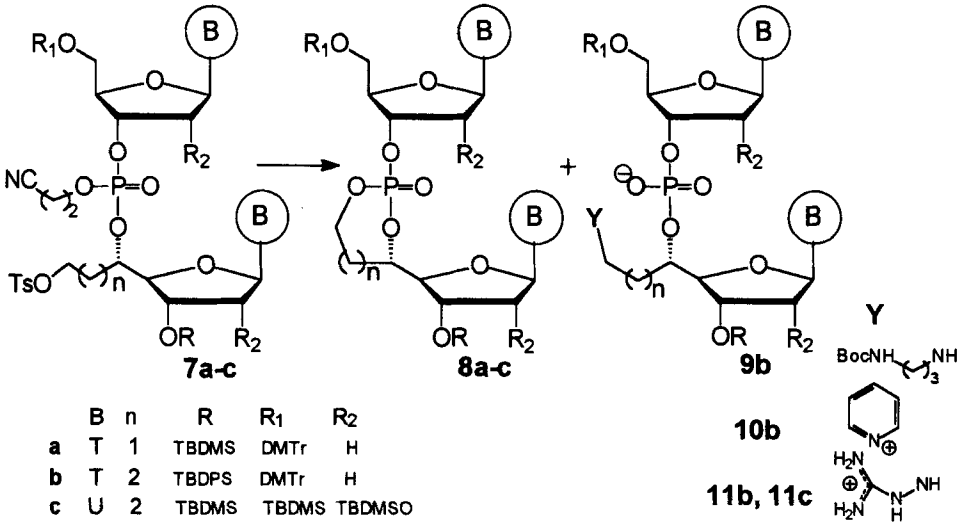
Synthesis

Tosyloxyethyl and tosyloxypropyl arms can be easily introduced at 5'-C with an "S" configuration for the new created asymetric carbon.[3] Starting from 5'-C-aldehyde thymidine, a Mukaiyama's reaction with the silylketene of methyl acetate catalysed[4] by $BiCl_3/ZnI_2$ provides compound **1** in 90% yield (scheme 1). Protection of the hydroxyl function at 5', followed by reduction of the ester function by diisobutylaluminium hydride produces 5'-C-hydroxyethyl thymidine **3** (80% for the two steps). On an other hand, 5'-C-allyl thymidine **2** is obtained in 90% yield using the Sakurai's methodology.[5] After trimethylsilyl protection of the 5' secondary hydroxyl function, an hydroboration/oxydation leads to 5'-C-hydroxypropyl thymidine **4**. Both **3** and **4** are submitted to tosylation of the primary hydroxyl function and acidic removal of the trimethylsilyl protective group, providing respectively **5** and **6** in 80% yield. It is noteworthy that the same reactions have been also applied to prepare 5'-C-hydroxypropyl uridine (not shown) from a 5'-C-aldehyde uridine protected at 2' and 3' with tertbutyldimethylsilyl groups.



Scheme 1

Three dimer models **7a-c** have been prepared using the phosphoramidite method (scheme2).



Scheme 2

In presence of an amine no coupling is observed with **7a** (tosyloxyethyl arm). The β-cyanoethyl protecting group is first removed allowing the intramolecular attack of the phosphate anion on the tosyl function and formation of a six membered cyclic phosphotriester **8a**. Treated with mono protected 1,3-diaminopropane **7b** gives **9b** and only traces of **8b**, in that case the seven membered cyclic phosphotriester is disfavored. When aminoguanidinium and **7b** are reacted in pyridine, the major adduct is the pyridinium conjugate **10b**. Both **11b** and **11c** are produced with traces of **8b** and **8c** when ethanol is used as solvent in the reaction of **7b** and **7c** with aminoguanidinium.

Conclusion

Depending on the length of the carbon chain substituted at 5'-C, cyclic phosphotriester bridge or conjugates can be prepared. The influence of a guanidinium (or pyridinium) internal counter ion on the hydrolysis of a phosphodiester bridge will be studied in ribo and deoxyribonucleotide series. Syntheses of 5'-C-substituted nucleoside phosphoramidites are on the way. Therefore 5'-C-tosyloxyalkylthymidines should be

versatile tools for the conjugation of nucleophile molecules with ODN's still on solid support.

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