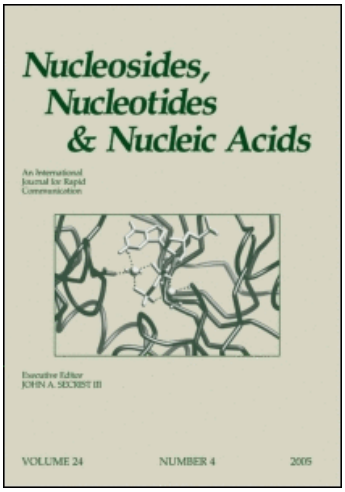


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A Convenient Synthesis of D-Psicofuranosyl Nucleosides[1]

Mallela S. P. Sarmastate[a]; Sreenivasulu Megati[a]; Robert S. Klein[a]; Brian A. Otter[a]
[a] Department of Oncology, Montefiore Medical Center, Albert Einstein College of Medicine Cancer Center and Medicinal Chemistry Laboratory, Bronx, NY

To cite this Article Sarmastate, Mallela S. P. , Megati, Sreenivasulu , Klein, Robert S. and Otter, Brian A.(1995) 'A Convenient Synthesis of D-Psicofuranosyl Nucleosides[1]', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 393 — 396
To link to this Article: DOI: 10.1080/15257779508012392
URL: http://dx.doi.org/10.1080/15257779508012392

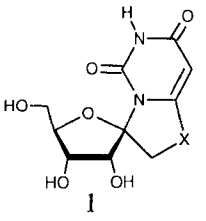
NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 393-396 (1995)

A CONVENIENT SYNTHESIS OF D-PSICOFURANOSYL NUCLEOSIDES[1]

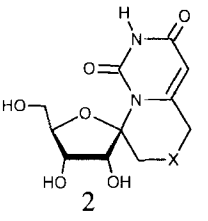
Mallela S. P. Sarma, Sreenivasulu Megati, Robert S. Klein and Brian A. Otter.

Albert Einstein College of Medicine Cancer Center and
Medicinal Chemistry Laboratory, Department of Oncology,
Montefiore Medical Center, Bronx, NY 10467

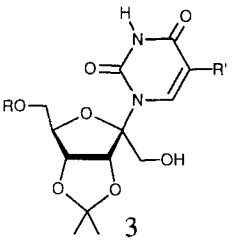
As part of our studies on the synthesis of conformationally restricted nucleosides of types **1** and **2** , where X = CH_2, O or S, we required access to differentially substituted D-



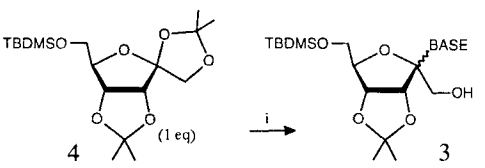
1



2



3



4 3

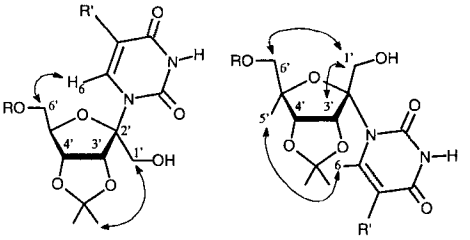
i) Silylated base (2 eq) and TMS-triflate (1.5 eq) in MeCN.

base	time	temp	yield
uracil	20h	20°	56%
5-ethyluracil	15h	20°	52%
5-hydroxyuracil	2h	0°	20%
5-bromouracil	90m	0°	67%
6-chloropurine	30m	0°	86%*

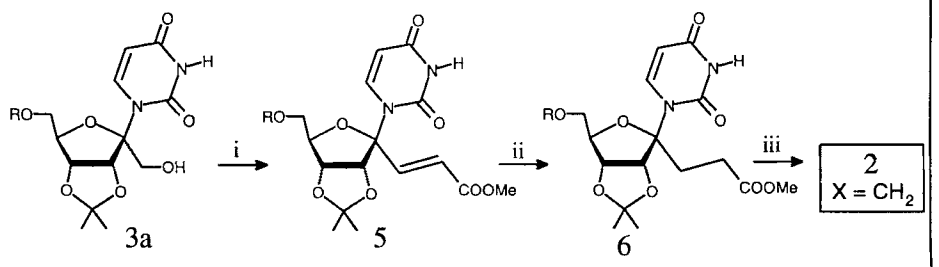
* isolated as the inosine analogues following treatment with sodium hydroxide.

psicofuranosyl nucleosides such as **3**. As shown in the table, we have developed a convenient approach to such compounds that depends on the direct condensation of the 1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose derivative **4** with an appropriate silylated purine or pyrimidine base. [2] Although the α and β anomers of **3** are formed in a 1:1 ratio, the yields of the β anomers are generally comparable with earlier condensation methods that use psicofuranosyl-halides,[3] 2-benzoates[4] or 2-nitro derivatives.[5] However, the present method has the advantage that the starting sugar **4** is more readily accessible. The precursor 6'-alcohol can be prepared in very large amounts from D-fructose using the method of Prisbe et al. [4]

The anomers of **3**, which are separable by chromatography, can be identified by empirical NMR methods analogous to those used for ribofuranosyl nucleosides. Thus the chemical shifts of the isopropylidene resonances in both the ^{1}H and ^{13}C spectra follow the patterns seen for their α and β ribosyl counterparts[6]. In addition, definitive identification of the α and β anomers of **3** has been made from the diagnostic NOE contacts shown at right. For both α and β compounds, the NOEs involving H-6 indicate a preference for conformations within the *anti* range, which are likely stabilized by hydrogen bonding between the 1'-OH and 2-oxo groups. Indeed, the 1'-hydroxyl resonances of both anomers (R = TBDMS) appear in $CDCl_3$ as double doublets rather than as the familiar triplets usually seen for primary hydroxyl groups, which is consistent with restricted rotation about the C-O bonds caused by hydrogen bonding. The widely disparate coupling constants $J_{1',OH}$ = 10.8 Hz and $J_{1'',OH}$ = 3.3 Hz typically seen for the α compounds indicate an overwhelming preference for a single hydroxyl rotamer.



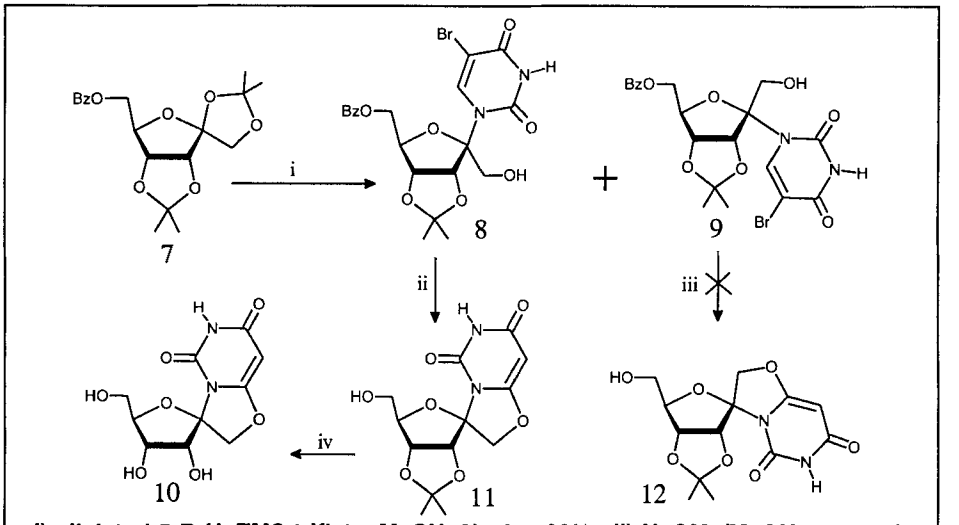
The ready availability of the uracil nucleoside **3a** has significantly shortened the route to the known[7] 6,1'-propanouridine (**2**, X = CH_2), as outlined in the panel below. Thus oxidation of the alcohol group of **3a** followed by a Wittig reaction to extend the C1'-chain affords alkene **5**. Reduction using transfer hydrogenation then leads to **6**, which has previously been converted into **2** (X = CH_2).[7]



R = TBDMS **i) DCC/DMSO/TFA/Pyr in EtOAc then Ph_3P=CHCOOMe in MeCN**
ii) 10% Pd-C and polymethylhydrosiloxane in EtOH, 60°, 3 days
iii) 4 steps, reference 7.

The synthesis of another spiro nucleoside (**10**) is illustrated in the final panel. In this case, condensation of the 6'-benzoate **7** with silylated 5-bromouracil affords a 1: **1** mixture of **8** and **9** in 90% yield. The separated β anomer **8** readily cyclizes to give the spiro nucleoside **11** on treatment with base. However, the α anomer **9** proved to be resistant to cyclization, even under more drastic conditions, since it affords only the 6'-debenzoylated product. The pronounced difference in reactivity between **8** and **9** means that treatment

of the mixed anomers with sodium methoxide followed by treatment with methanolic HCl affords **10** as the only nucleoside product. Apparently the uncyclized α anomer undergoes destructive hydrolysis while the spiro nucleoside **10** survives.



i) silylated 5-BrU, TMS-triflate, MeCN, 2h, 0 °, 90%. ii) NaOMe/MeOH, 60 °, 15h iii) As ii) except several days. iv) 12% HCl-MeOH

Other than **2** (X = CH_2) and **10** described above, only a few spiro nucleosides have been reported. These include the spiro cyclocytidine corresponding to **1** (X = O),[8] and, very recently, the 2'-deoxy version of **1** (X = CH_2).[9] Since they have the same tautomeric structures as ordinary nucleosides – and hence bear a full complement of unmodified hydrogen bonding groups – *syn* spiro nucleosides and nucleotides of types **1** and **2** are potentially useful for probing the conformational specificities of the enzymes of nucleic acid metabolism. The overall conformations of these molecules, and particularly the glycosyl rotation angles χ (O5'-C2'-N1-C2), depend largely upon the conformations of the C2'-fused spiro rings, and molecular modeling studies suggest that a good deal of flexibility is maintained. For example, Hyperchem™ (based on MM2 force field) indicates two energy minima for **10** (χ = 50° and 80°) in both the 3'-endo (S) and 4'-endo(N) sugar puckers and for each of the three rotational states (+sc, ap and -sc) of the primary hydroxy group. While the global minimum is associated with the combination 4'-endo/ χ=80°/ ap (or -sc), the difference in energy between the various minima is predicted to be only about 2 Kcal/mole, so it is likely that all of these conformations will be populated to some extent.

In solution (DMSO-d_6), the $J_{4',5'}$ value of 2.3 Hz observed for **10** indicates a decided preference for S sugar puckering. Conformational information is again provided by the multiplicity of the hydroxyl resonance, which appears as a double doublet with $J_{6',OH}$ and $J_{6'',OH}$ values of 5.4 and 6.6 Hz, respectively. Although rotation about the C6'-O bond of **10** is not nearly as restricted as that of the α-isopropylidene nucleosides described earlier,

the observed splitting is consistent with hydrogen bonding between the 2-oxo and 6'-OH groups for at least a sub-population of +sc conformers. For such H-bonded conformers, χ would probably tend towards 50° rather than 80°.

REFERENCES

1) Support of this investigation by NIH grant CA54272 and the Cancer Center Support Grant CA13330 is gratefully acknowledged.
2) The inspiration for this reaction came from the recent report that certain 6-substituted-1,2:3,4-di-*O*-isopropylidene-D-psicofuranose derivatives can be induced to undergo intramolecular N-C bond formation at C2: See P. Chemla. Stereoselective Synthesis of (+)-Hydantocidin. *Tetrahedron. Lett.* **1993**, *34*, 7391-7294.
3) See: E. Lukevics and A. Zablocka, "Nucleoside Synthesis Organosilicon Methods", Ellis Horwood Ltd., London **1991**.
4) E. J. Prisbe, J. Smejkal, J. P. H. Verheyden and J. G. Moffat. *J. Org. Chem.*, **1976**, *41*, 1836-1846.
5) K. Mahmood, A. Vasella and B. Bernet. *Helv. Chim. Acta*, **1991**, *74*, 1555-1584.
6) J-L. Imbach, *Ann. New York Acad. Sci.*, **1975**, *255*, 177; H. Ohrui, G. H. Jones, J. G. Moffat, M. L. Maddox, A. T. Christensen and S. K. Byram. *J. Am. Chem. Soc.*, **1975**, *97*, 4602; G. Trummlitz, D. B. Repke and J. G. Moffat. *J. Org. Chem.*, **1975**, *40*, 3352; T. J. Cousineau and J. A. Secrist III, *ibid*, **1979**, *44*, 4351.
7) Y. Yoshimura, B. A. Otter, T. Ueda and A. Matsuda. *Chem. Pharm. Bull.*, **1992**, *40*, 1761-1769.
8) S. G. Zavgorodny. *Tetrahedron lett.*, **1981**, *22*, 3003-3006.
9) A. Kittaka, H. Tanaka, Y. Odanaka, K. Ohnuki, K. Yamaguchi and T. Miyasaka. *J. Org. Chem.*, **1994**, *59*, 3636-3641.