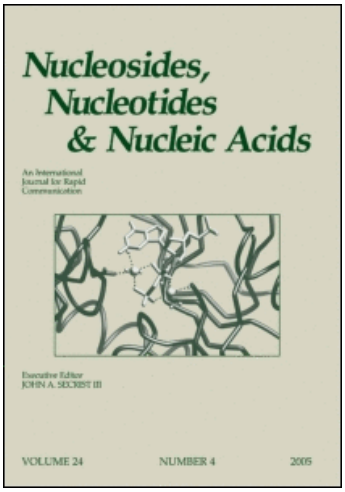


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Systematic Synthesis and Biological Evaluation of α - and β-D-Xylo- and Lyxofuranonucleosides of the Five Naturally Occurring Nucleic Acid Bases

G. Gosselin[a]; M. C. Bergogne[a]; J. L. Imbach[a]; J. De Rudder[b]; E. De Clercq[c]
[a] Laboratoire. de Chimie Bioorganique, Montpellier Cedex, France [b] Synthelabo, France [c] Rega Institute. for. Medical Research., Katholieke Universiteit Leuven, Leuven, Belgique

To cite this Article Gosselin, G. , Bergogne, M. C. , Imbach, J. L. , De Rudder, J. and De Clercq, E.(1987) 'Systematic Synthesis and Biological Evaluation of α - and β-D-Xylo- and Lyxofuranonucleosides of the Five Naturally Occurring Nucleic Acid Bases', Nucleosides, Nucleotides and Nucleic Acids, 6: 1, 65 — 72
To link to this Article: DOI: 10.1080/07328318708056180
URL: http://dx.doi.org/10.1080/07328318708056180

NUCLEOSIDES & NUCLEOTIDES, 6(1&2), 65-72 (1987)

SYSTEMATIC SYNTHESIS AND BIOLOGICAL EVALUATION OF α- AND β-D-XYLO- AND LYXOFURANONUCLEOSIDES OF THE FIVE NATURALLY OCCURRING NUCLEIC ACID BASES

G. Gosselin[1], M.-C. Bergogne[1], J.-L. Imbach[1]*, J. De Rudder[2] and E. De Clercq[3].

[1]*Laboratoire de Chimie Bioorganique, UA CNRS 488, U.S.T.L., 34060 Montpellier Cedex (France) ;*

[2]*Synthélabo, 92350 Le Plessis-Robinson (France);*

[3]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven (Belgique).*

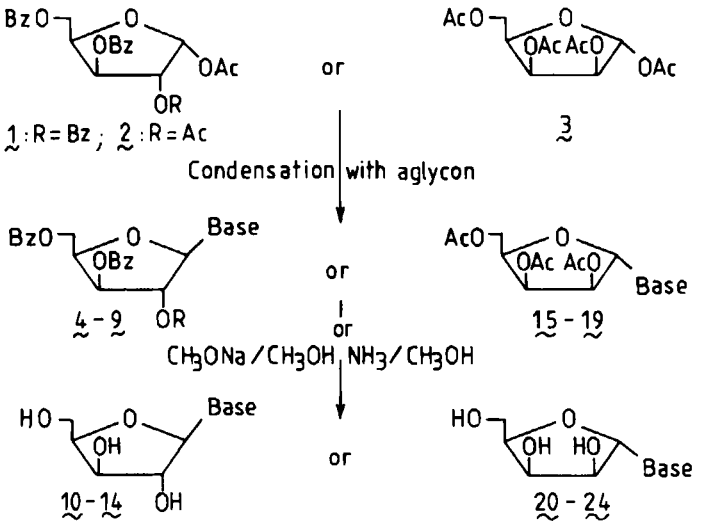
Abstract. The α- and β-D-Xylofuranosyl and -lyxofuranosyl analogues of the five naturally occurring nucleic acid bases have been the subject of a systematic synthesis and examination of some of their biological properties, i.e. antiviral, antimetabolic and cytostatic activities.

Introduction. During the last decades there has been considerable interest in nucleosides modified on the sugar moiety as potential antiviral and antitumor agents.[1] In order to define structure-activity relationships we initiated a comprehensive program to systematically study anomeric D-pentofuranosyl nucleosides.[2,3] Here we present recent results concerning the synthesis and some biological properties of anomeric D-xylo-,[4] and -lyxofurananonucleosides.[5]

Chemistry.

Synthesis of β-D-Xylofuranosyl 10-14 and α-D-Lyxofuranosyl nucleosides 20-24.

In accord with Baker's rule,[6] condensations of suitably protected 2'-O-acyl-D-pentofuranoses and purine or pyridimine bases were employed to prepare these *trans*-1',2' nucleosides. As starting sugars we used interchangeably 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-xylofuranose (1)[7-9] or 1,2-di-O-acetyl-3,5-di-O-benzoyl-α-D-xylofuranose (2)[10] in the xylose series and tetra-O-acetyl-α-D-lyxofuranose (3)[11] in the lyxose series.



SCHEME 1

Glycosylations were effected by the best procedures found in the literature for each aglycon. All protected β-D-xylo- 4-9 and α-D-lyxofuranonucleosides 15-19 were isolated in moderate to satisfactory yields after purification by silica gel column chromatography (*Table 1*). Removal of the acyl blocking groups with methanolic ammonia or methanolic sodium methoxide then afforded the desired unprotected derivatives 10-14, 20-24.

Synthesis of α-D-Xylofuranosyl 28-32 and β-D-Lyxofuranosyl nucleosides 36a-e.

A priori, three methods can be envisaged in the two series for the preparation of these *cis*-1',2' nucleosides : a) glycosylation with a suitably protected D-xylo- or lyxofuranose having in its 2-O- position a non-participating group ; b) constructing, as in other series,[17] the heteroxyclic moiety from a D-xylose or lyxose derivative possessing a 2-oxazoline ring fused in the *cis*-1',2' configuration ; c) epimerisation of the 2' or 3'-position, respectively of a α-D-lyxo- or α-D-ribofuranonucleoside derivative in the xylose series and of a β-D-xylo- or β-D-arabinofuranonucleoside derivative in the lyxose series. We discarded the first possibility owing to its lack or regioselectivity and stereospecificity.

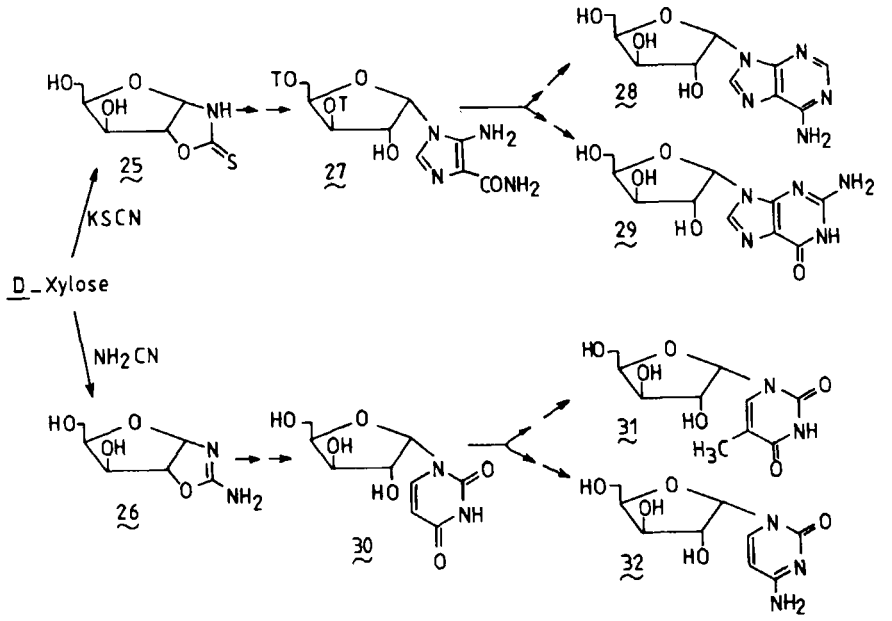
In the xylose series (*Scheme 2*), total synthesis approaches were considered.[4] As starting materials, the xylofuranothioxooxazolidine (25)

TABLE 1. Preparation of β-D-Xylo- and α-D-Lyxofuranonucleosides.

	Starting		N-9 purine or N-1 pyrimidine protected nucleosides			Unprotected nucleosides		
	Sugar	Base	Condensation procedure[a]		Yield[b]	Deblocking procedure[c]		Yield (from protected nucleosides)
β-D-Xylofuranonucleosides	1	Thymine	A	4	72 %	E	10	51 %
	1	Cytosine	B	5	33 %	E	11	74 %
	2	Silylated cytosine	C	6	75 %	F	11	76 %
	2	Uracil	A	7	82 %	E	12	77 %
	2	Adenine	B	8	70 %	E F	13	75 % 78 %
	2	N^2-acetyl guanine	D	9 : R=H[d] 59 % (+ N-7 isomer, 19%)		E	14	70 %
α-D-Lyxofuranonucleosides	3	Thymine	A	15	60 %	F	20	66 %
	3	Cytosine	B	16	31 %	F	21	68 %
	3	Uracil	A	17 (+ N-3 isomer + N-1,N-3 bis-lyxoside)	49 %	E	22	64 %
	3	Adenine	B	18 : quantitative		F	23	72 %
	3	Silylated N^2-acetyl guanine	C	19 (+ N-7 isomer, 14 %)	33 %	E	24	61 %

[a] A = HMDS, TMSCl, $SnCl_4$ / CH_3CN ;[12] B = $SnCl_4/CH_3CN$;[9,13] C = TMSTF/ $ClCH_2CH_2Cl$;[14] D = BSA, TMSTF/CH_3CN.[15,16]

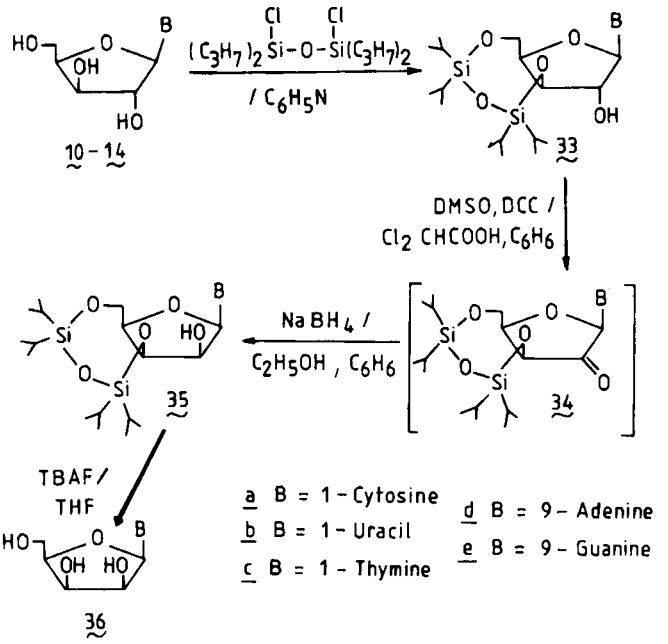
[b] After silica gel column chromatography purification with appropriate eluents. [c] E = CH_3ONa/CH_3OH ; F = NH_3/CH_3OH. [d] Separation from its N-7 isomer could be achieved only after selective 2'-O-deacetylation by hydrazine hydrate.



SCHEME 2 (T = TBDMS)

and the 2-aminooxazoline (26) were prepared from D-xylose. For the synthesis of α-D-xylofuranosyl purine nucleosides, 25 was first transformed to the α-Xylo AICA derivative 27 and then cyclized to α-xyloA (28) and α-XyloG (29) with minor modification of published procedures in other series. For the synthesis of α-D-xylofuranosyl pyrimidine nucleosides, 26 was transformed to α-XyloU (30) via the O^2,O^2-anhydro-1-α-D-xylofuranosyluracil. α-XyloU (30) was then converted in α-XyloT (31) by Mannich reaction with formaldehyde and piperidine, and in α-XyloC (32) by amination of its 4-thio derivative.

In the lyxose series, building the heterocyclic moiety was excluded owing to the failure of D-lyxose to cyclise to a pentofuranooxazoline.[18-21] Thus we turned to another approach, consisting of a 2'-selective oxidation of a suitably protected β-D-xylofuranonucleoside, followed by reduction of the intermediate 2'-keto derivative with sodium borohydride (*Scheme* 3).[5] As 3',5'-O-protecting groups, the TPDS group of Markiewicz[22] was considered the best choice in view of its high 3',5' selectivity. Oxidation of the 3',5'-O-(TPDS) derivatives 33 was effected using the Pfitzner-Moffatt reagent (DMSO/DCC) with dichloroacetic acid as the proton



SCHEME 3

source.[23] Purification of the furan-2'-ulosides 34 was not attempted and the crude reaction mixtures were directly treated with sodium borohydride at 0°C. The expected protected β-D-lyxofuranonucleosides 35 were isolated in moderate yields after silica gel column chromatography. Desilylation of 35 was achieved with TBAF in THF and gave the desired β-D-lyxofuranonucleosides 36 after chromatographic purification.

Structural assignments for all anomeric D-xylo- and lyxofuranonucleosides were based on elemental analysis and their physical properties. For previously described compounds, our data were in accord with literature values, except for α-XyloA (28).[24]

Biological evaluation.[4,5]

All the prepared α- and β-D-xylo- and lyxofuranonucleosides 28-32, 10-14, 20-24 36a-e were evaluated *in vitro* against various viruses (DNA viruses : herpes simplex-1 and 2, vaccinia ; (±)RNA viruses = reovirus-1; (+)RNA virus = rhino-1A and 9, sindbis, semliki forest, coxsackie-B4, polio-1 ; (-)RNA viruses : vesicular stomatitis, parainfluenza-3) in

four cell systems (primary rabbit kidney, Hela, African green monkey kidney (Vero B) and human diploid (WI-38) cells). From these studies it is apparent that four compounds, namely β-XyloA (13), β-XyloG (14), β-XyloC (11) and α-LyxoA (23) exhibited significant antiviral activity against DNA viruses. The antiherpetic activity of β-XyloA (13)[25,27] and β-XyloG (14)[28] has been previously noted as have been the antitumor properties of 13.[29-31] We have also ascertained that 13 and 14 brought about a marked suppression of the proliferation of mouse myeloma cells SP2 ;[4] however *in vivo* LD_{50} (50 % lethal dose) of these compound was found rather low.

Most promising were β-XyloC (11) and α-LyxoA (23). *In vitro,* none of these two compounds caused a microscopically detectable alteration of host-cell morphology at a concentration of 200 or 400 µg/ml. β-XyloC (11) exhibited a distinct antiviral activity against DNA viruses (HSV-1 and 2, vaccinia) and α-LyxoA (23) against the same DNA viruses and also against one (+)RNA virus (coxsackie) and one (-)RNA virus (parainfluenza-3). *In vivo* 11 and 23 were remarkably nontoxic : LD_{50} > 2 g/kg, and they protected hairless (hr/hr) mice against several parameters (lesions, paralysis and death) of a cutaneous HSV-1 or HSV-2 infection. Furthermore, findings with a rather small number (six) of animals per group indicate that these two compounds might be effective against herpetic encephalitis in mice at subtoxic doses.

Although preliminary, our results point to the effectiveness of β-XyloC (11) and α-LyxoA (23) in various infection models. Additional studies have been planned now to establish both the basis of the antiviral activity and the chemotherapeutic potency of these two compounds.

Abbreviations : Bz, benzoyl ; Ac, acetyl ; HMDS, hexamethyldisilazane ; TMSCl, trimethylchlorosilane ; TMSTF, trimethylsilyl trifluoromethanesulfonate ; BSA, bis(trimethylsilyl) acetamide ; TBDMS, *tert*-butyldimethylsilyl ; TPDS, 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl ; DMSO, dimethylsulfoxide ; DCC, N,N'-dicyclohexylcarbodiimide ; TBAF, tetra-n-butylammonium fluoride ; THF, tetrahydrofuran.

REFERENCES

1. *"Nucleoside Analogues : Chemistry, Biology and Medical Applications"*; R.T. WALKER, E. De CLERCQ and F. ECKSTEIN, Eds., Nato Advanced Study Institutes Series : Series A, Life Sciences Vol. 26 ; Plenum Press : New York (1979).

2. J.-L. IMBACH, G. GOSSELIN and J. De RUDDER, *French Patent* FR 2,528, 311 (Cl. AGIK 31/70) : *Chem. Abstr.*, *100*, 197792x (1984).

3. J. De RUDDER, J. LECLERC, M. MERCIER, G. GOSSELIN and J.-L. IMBACH, *Nucleosides, Nucleotides*, *4*, 221 (1985).

4. G. GOSSELIN, M.-C. BERGOGNE, J. De RUDDER, E. De CLERCQ and J.-L. IMBACH, *J. Med. Chem.*, *29*, 203 (1986).

5. G. GOSSELIN, M.-C. BERGOGNE, J. De RUDDER, E. De CLERCQ and J.-L. IMBACH, *J. Med. Chem.*, *in press* (1987).

6. B.R. BAKER, in *"The Ciba Foundation Symposium on the Chemistry and Biology of the Purines"* ; G.E.W. WOLSTENHOLME and C.M. O'CONNOR Eds.; Churchill : London (1957), p. 120.

7. J.J. FOX, N. YUNG, J. DAVOLL and G.B. BROWN, *J. Am. Chem. Soc.*, *78*, 2117 (1956).

8. T. THACZYNSKI, J. SMEJKAL and F. SORM, *Collect. Czech. Chem. Commun.*, *29*, 1736 (1964).

9. C. NAKAYAMA and M. SANEYOSHI, *Nucleosides, Nucleotides*, *1*, 139 (1982).

10. G. GOSSELIN and J.-L. IMBACH, *J. Heterocycl. Chem.*, *19*, 597 (1982).

11. B.L. KAM, J.L. BARASCUT and J.L. IMBACH, *Carbohydr. Res.*, *69*, 135 (1979).

12. H. VORBRUGGEN and B. BENNUA, *Tetrahedron Lett.*, 1339 (1978) ; *Chem. Ber.*, *114*, 1279 (1981).

13. M. SANEYOSHI and E. SATOH, *Chem. Pharm. Bull.*, *27*, 2518 (1979).

14. H. VORBRUGGEN, K. KROLIKIEWICZ and B. BENNUA, *Chem. Ber.*, *114*, 1234 (1981).

15. G.E. WRIGHT and L.W. DUDYCZ, *J. Med. Chem.*, *27*, 175 (1984).

16. L.W. DUDYCZ and G.E. WRIGHT, *Nucleosides, Nucleotides*, *3*, 33 (1984).

17. For a literature survey of this approach, *see ref. 4*.

18. J.C. JOCHIMS, A. SERLIGER and G. TARGEL, *Chem. Ber.*, *100*, 845 (1967).

19. A. HOLY, *Nucleic Acids Res.*, *1*, 289 (1974).

20. F.G. GONZALEZ, M.G. GUILLEN, J.A.G. PEREZ and E.R. GALAN, *Carbohydr. Res.*, *80*, 37 (1980).

21. P. BRIARD, R. ROQUES, G. GOSSELIN, J.L. IMBACH, J.L. MONTERO, J.P. DECLERCQ and G. GERMAIN, *Acta Cryst.*, *B-38*, 1027 (1982).

22. W.T. MARKIEWICZ, *J. Chem. Res., Synop.*, 24 (1979) ; *J. Chem. Res. Miniprint*, 181 (1979).

23. V. BRODBECK and J.G. MOFFATT, *J. Org. Chem.*, *35*, 3552 (1970).

24. For a discussion, *see ref. 4*.

25. J. De RUDDER, F. ANDREEFF and M. PRIVAT DE GARILHE, *C.R. Hebd. Seances Acad. Sci., Ser. D, 264, 677 (1967)* ; J.R. BOISSIER, P. LEPINE, J. De RUDDER, M. PRIVAT DE GARILHE, *French Patent* FR.M.6, *164.Cl.* A *61k, C 07d* : *Chem. Abstr., 72, 44073s (1970).*

26. D.A. EPPSTEIN, J.W. BARNETT, Y.V. MARSH, G. GOSSELIN and J.L. IMBACH, *Nature, (London), 302, 723 (1983).*

27. B.B. GOSWAMI, G. GOSSELIN, J.L. IMBACH and O.K. SHARMA, *Virology, 137, 400 (1984).*

28. G.R. REVANKAR, J.H. HUFFMAN, R.W. SIDWELL, R.L. TOLMAN, R.K. ROBINS and L.B. ALLEN, *J. Med. Chem., 19, 1026 (1976).*

29. D.B. ELLIS and G.A. LEPAGE, *Mol. Pharmacol., 1, 231 (1965)* ; G.A. LEPAGE, *Adv. Enzyme Regul., 8, 323 (1970).*

30. P. ROY-BURMAN, *Recent Results Cancer Res., 25, 1 (1970)* ; P. ROY-BURMAN, "*Analogues of Nucleic Acid Components. Mechanisms of Action*"; Springer-Verlag : Berlin, Heidelberg, pp. 34-35 (1970).

31. C.E. CASS, M. SELNER, T.H. TAN, W.H. MUHS and M.J. ROBINS, *Cancer Treat. Rep., 66, 317 (1982).*