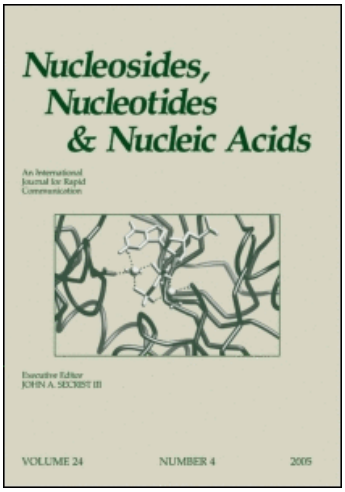

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Biological Properties of ( ) and (-)-(E)-5-(2-bronovinyl)-2[1] -deoxy-1[1] a-Carbauridine

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To cite this Article Balzarini, Jan , Baumgartner, Harald , Bodenteich, Michael , De Clercq, Erik and Griengl, Herfried(1989) 'Synthesis and Biological Properties of ( ) and (-)-(E)-5-(2-bronovinyl)-2[1] -deoxy-1[1] a-Carbauridine', Nucleosides, Nucleotides and Nucleic Acids, 8: 5, 855 — 858
To link to this Article: DOI: 10.1080/07328318908054229
URL: http://dx.doi.org/10.1080/07328318908054229

NUCLEOSIDES & NUCLEOTIDES, 8(5&6), 855-858 (1989)

SYNTHESIS AND BIOLOGICAL PROPERTIES OF (+)- AND (-)-(*E*)-5-(2-BROMOVINYL)-2'-DEOXY-1'a-CARBAURIDINE

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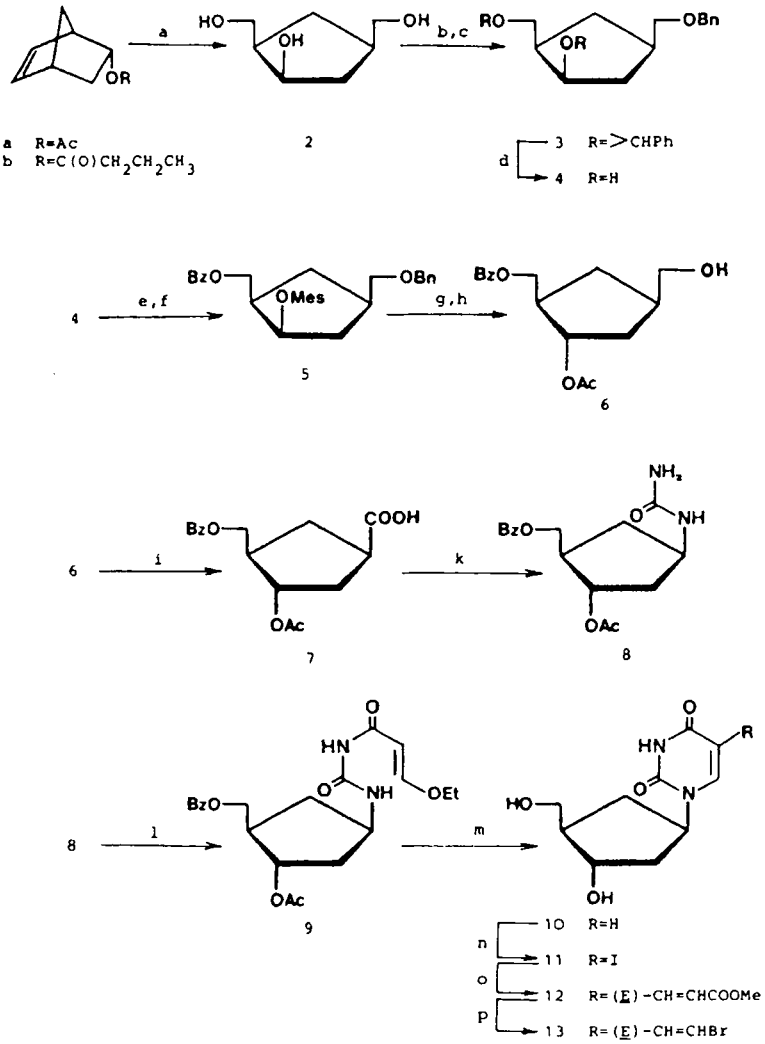
Abstract: Carbocyclic (+)- and (-)-(*E*)-5-(2-bromovinyl)-2'-deoxyuridine have been prepared from (+)- and (-)-*endo*-norborn-5-en-2-yl butyrate. In cell cultures both (+)- and (-)-C-BVDU showed activity against herpes simplex virus types 1 and 2, (+)-C-BVDU being only slightly less active than BVDU itself. (-)-C-BVDU gave a smaller but still significant antiviral effect. A nomenclature for carbocyclic nucleosides is proposed.

Recently, carbocyclic nucleosides, in which the D-ribose moiety of the nucleoside is replaced by a cyclopentane system, have gained increasing interest[1]. In these compounds the N-glycosidic linkage, which is prone to hydrolysis, is replaced by a more stable bond. In some cases, adenosine-type carbocyclic nucleosides were found resistant towards the action of adenosine deaminase[2]. For these reasons biostability and bioavailability are enhanced. The biological properties of carbocyclic nucleosides are very often similar to those of 'genuine' nucleosides with reduced biological activity in most cases (see, e.g., refs.[4-7]). However, examples are known where the carba-derivative is the more potent compound (see, e.g., refs.[8,9]). With respect to biological properties the enantiomers of carbocyclic nucleosides are expected to be different. Therefore, the carbocyclic analogue of the potent antiviral compound (*E*)-5-(2-bromovinyl)-2'-deoxyuridine[10] has been synthesized in both enantiomeric forms.

The synthetic strategy used has already been published as a short communication[11] for (+)-C-BVDU, the enantiomer with the 'natural' configuration, which is drawn in the formula scheme. Either (+)-*endo*-norborn-5-en-2-yl butyrate [for the synthesis of (+)-C-BVDU] or the (-)-enantiomer [for the synthesis of (-)-BVDU] were used as starting materials, obtained from the racemate by enzymatic resolution with *Candida cylindracea* lipase[12]. In the 'natural' series compounds 2-5 are levorotatory, compounds 6-13 dextrorotatory. After recrystallisation of the monobenzyl derivative 4 both enantiomers were obtained with constant optical rotations. Therefore, compounds 4 - 13 and the 'unnatural' enantiomeric forms *ent*-4 - *ent*-13 were considered to be enantiomerically pure.

Data for the antiviral activity are given in Table 1. (+)-C-BVDU showed a slightly reduced antiviral effect (HSV-1, HSV-2) as compared to BVDU. Interestingly, this activity



[a] O_3, MeOH, -70°C; $LiAlH_4$, THF [b] $PhCH(OMe)_2$, HBF_4, DMF [c] KH, THF, $PhCH_2Br$
[d] aq.H_2SO_4, 100°C [e] BzCl, Pyr, CH_2Cl_2 [f] MesCl, Et_3N, CH_2Cl_2 [g] CsOAc, DMSO, 40-45°C [h] Pd-C, EtOH [i] PDC, DMF, r.t. [k] DPPA, C_6H_6, NH_3
[l] 3-ethoxyacryloyl chloride, Pyr, CH_2Cl_2 [m] aq.NH_3, 90°C, 4h
[n] I_2, 0.75N HNO_3, dioxane, reflux, 1h [o] methylacrylate, dioxane, $Pd(OAc)_2$ Ph_3P, Et_3N, 85°C, 15h [p] 1.8N KOH, r.t., 2h; $KHCO_3$, NBS, DMF, r.t.

SCHEME 1

TABLE 1. Antiviral activity of carbocyclic BVDU enantiomers in primary rabbit kidney cell cultures

Compound	Minimum inhibitory concentration μg/ml*						
	Herpes simplex virus-1 (KOS)	Herpes simplex virus-1 (F)	Herpes simplex virus-1 (McIntyre)	Herpes simplex virus-2 (G)	Herpes simplex virus-2 (196)	Herpes simplex virus-2 (Lyons)	Vaccinia virus
(-)-C-BVDU	0.7	10	10	20	100	100	>400
(+)-C-BVDU	0.05	0.02	0.02	7	100	20	>400
(±)-C-BVDU	0.02	0.06	0.07	7	70	20	>400
BVDU	0.01	0.01	0.01	2	70	7	15

* Required to reduce virus induced cytopathogenicity by 50%. The data represent average values for 3 to 4 seperate experiments.

TABLE 2. Nomenclature of carbocyclic pentofuranoses and carbocyclic nucleosides

Compound	Definite rules (IUPAC)	Carbohydrate nomenclature + Natural Products Recommendation 1976
2	(-)-(1*R*,3*R*,4*R*)-4-Hydroxycyclopentane-1,3-dimethanol	(-)-2-Deoxy-1a-carba-β-D-*threo*-pentofuranosylmethanol [(-)-2,5-Anhydro-3-deoxy-2a-carba-D-*xylo*-hexitol]
3	(-)-(1*R*,6*R*,8*R*)-8-Benzyloxymethyl-3-phenyl-2,4-dioxabicyclo[4.3.0]-nonane	(-)-3,5-O-Benzylidene-2-deoxy-1a-carba-β-D-*threo*-pentofuranosyl-methanol [(-)-2,5,Anhydro-4,6-O-benzylidene-3-deoxy-2a-carba-D-*xylo*-hexitol]
5	(-)-(1*R*,2*R*,4*R*)-2-Benzoyloxymethyl-4-benzyloxymethylcyclopentyl-methanesulfonate	(-)-5-O-Benzoyl-2-deoxy-3-O-methyl-sulfonyl-1a-carba-β-D-*threo*-pento-furanosylmethyl benzyl ether [(-)-2,5-Anhydro-6-O-benzoyl-1-O-benzyl-3-deoxy-4-O-methylsulfonyl-2a-carba-D-*xylo*-hexitol]
6	(+)-(1*R*,3*S*,4*R*)-3-Acetoxy-4-benzoyloxymethylcyclo-pentanemethanol	(+)-3-O-Acetyl-5-O-benzoyl-2-deoxy-1a-carba-β-D-*erythro*-pentofuranosyl-methanol [(+)-4-O-Acetyl-2,5-anhydro-6-O-benzoyl-3-deoxy-2a-carba-D-*ribo*-hexitol]
10	(+)-1-[(1*R*,3*S*,4*R*)-3-Hydroxy-4-hydroxymethylcyclopentyl]-1*H*,3*H*-pyrimidin-2,4-dione	(+)-2'-Deoxy-1'a-carbauridine
13	(+)-1-[(1*R*,3*S*,4*R*)-3-Hydroxy-4-hydroxymethylcyclopentyl]--5-[(*E*)-2-bromovinyl]-1*H*,3*H*-pyrimidin-2,4-dione	(+)-5-(*E*)-(2-bromovinyl)-2'-deoxy-1'a-carbauridine

is quite similar to that for the racemate. It has to be pointed out that for some strains of HSV-1 (KOS) and HSV-2 (G) also (-)-C-BVDU, possessing the 'unnatural' configuration, showed a marked antiviral effect. No antiviral activity against TK⁻ HSV-1 strains (B 2006, VMW 1837) could be detected with either (+)- or (-)-C-BVDU at concentrations up to 400 µg/ml. Therefore, phosphorylation by viral thymidine kinase must be a prerequisite for the antiviral action of (+)- and (-)-C-BVDU. With respect to the kinetics (+)-C-BVDU showed competitive inhibition, whereas (-)-C-BVDU interacted in a linear mixed-type competitive manner. Up to a concentration of 400 µg/ml (+)- and (-)-C-BVDU had no activity against vaccinia virus and vesicular stomatitis virus, nor were they cytotoxic at concentrations up to 400 µg/ml.

Nomenclature of enantiomerically pure carbocyclic nucleosides is a difficult task, since application of the sequence rule for the configuration of the chiral centers does not lead to chemical names, where the structure can be deduced without using paper and pencil. Application of the IUPAC-recommendations for the nomenclature of cyclitols[13] also is unsatisfactory. To circumvent these obstacles we suggest a more strict use of the already familiar 'carba'-nomenclature for carbocyclic nucleosides and carbocyclic pentofuranoses where according to rules F-4.12 and F-4.13 of 'General Principles for the Naming of Natural Products and Related Compounds (Provisional Recommendations 1976)'[14,15] replacement of the ring oxygen is characterized by the term 'carba' within the chemical name according to carbohydrate nomenclature[16]. Examples for this use are given in Table 2. For a maximum of comprehensible structural information we would prefer a more deliberate use of the rules over a too rigid application (given in parentheses).

Acknowledgement: Financial support by grants from the Belgian Fonds voor Geneeskundig Wetenschappelijk Onderzoek (project no.3.0037.83 and 3.0097.87), the Belgian Geconcerteerde Onderzoeksacties (project no.85/90-79) and by Fonds zur Förderung der wissenschaftlichen Forschung (project no.P6030C) is gratefully acknowledged.

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