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A Short, Convergent Synthesis of Two Chiral Antiviral Agents, (+) Carbocyclic 2'-Deoxy-5-[(E)-2-Bromovinyl] Uridine and (+) Carbocyclic 2'-DeoxyGuanosine

Alan D. Borthwick*, Andrew J. Crame, Anne M. Exall, Gordon G. Weingarten and Mahmuod Mahmoudian+.

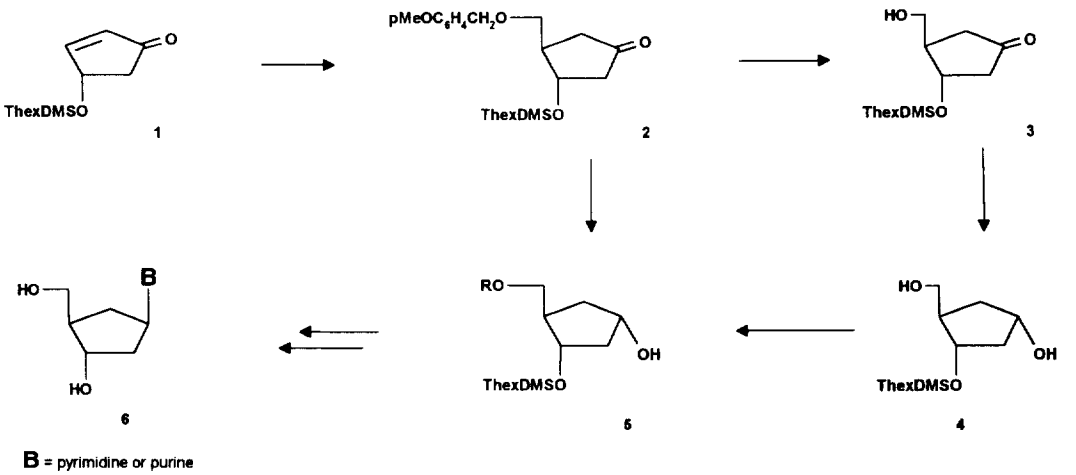
Departments of Medicinal Chemistry II and Natural Products+, Glaxo Research and Development Ltd, Glaxo Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY. UK.

Abstract: Stereoselective microbial reduction of ketone **2** gave the alcohol **5** which was coupled under Mitsunobu conditions with the protected pyrimidine **7** and purine **10** to give on deprotection the chiral antiviral nucleosides (+) carbocyclic 2'-deoxy-5-[(E)-2bromovinyl] uridine **9** and (+) carbocyclic 2'-deoxyguanosine **12.**

Two antiviral agents of current interest are the chiral carbocyclic 2'-*deoxyribo*nucleosides (+) carbocyclic 2'-deoxy-5-[(E)-2-bromovinyl] uridine (+ C-BVDU) and (+) carbocyclic 2'-deoxyguanosine (+ C-DG). The pyrimidine nucleoside (+) C-BVDU, GR95168 possesses activity against herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV, chicken pox and shingles) *in vitro*[1] and *in vivo*,[2,3] while the purine nucleoside (+) C-DG has a complementary antiviral spectrum of activity against herpes simplex virus type 2 (HSV-2),[4] human cytomegalovirus (HCMV)[5] and hepatitis B virus (HBV).[6]

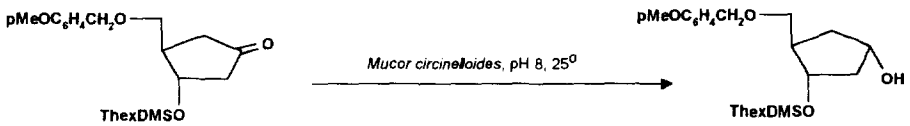
In a previous communication[7] we reported a four step synthesis of a chiral carbocyclic 2'-*deoxyribo*nucleoside synthon **5** (R = Ph_3C) starting from (4S)-4 -(thexyldimethylsilyloxy)-2-cyclopenten-1-one **1**, which is part of our strategy to obtain a short, efficient and convergent synthesis of chiral carbocyclic 2'-*deoxyribo*nucleosides **6** (Scheme 1).

Scheme 1



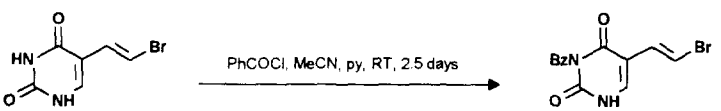
An important feature of this synthesis was the stereoselective, directed 1,4-reduction of the hydroxycyclopentanone **3** to the diol **4** using $NaBH(AcO)_3$. It was reasoned that this route could be shortened by the stereoselective reduction of cyclopentanone **2** directly to the α-alchohol **5** using a microorganism where chemically this had failed.[7] In an attempt to achieve this we have investigated a number of microorganisms (yeasts, bacteria, fungi, *Streptomyces* spp.) for their ability to reduce the cyclopentanone **2** stereoselectively to the α-alchohol **5** (Scheme 2). Two fungal strains, *Mucor racemosus* and *Mucor circinelloides,* produced **5** as the predominant product. Production was, however, best with the latter organism and the formation of other metabolites was also much less pronounced. Various parameters were optimised to improve the conversion. The optimum pH was found to be 8.0, production of **5** was very much lower at pH 7.0. The ideal temperature was established as 25°C. Interestingly, production of the corresponding β-isomer of **5** was significant at higher temperatures. Optimisation of the culture age and time of substrate addition resulted in a significant improvement in production of **5**. Increasing the substrate concentration to 5g/ L also increased the production rate. Under these conditions,[8] *M. circinelloides* catalysed the asymmetric reduction of **2** to afford **5** in 62% yield (de>98%).

Scheme 2



2 **5**

Recent reports suggest that the coupling of suitably protected nucleoside bases with cyclopentanol derivatives such as **5** is best achieved using Mitsunobu conditions rather than by displacement of a tosylate or mesylate.[9] We have used this methodology to couple N-3 benzoyl, 5-bromovinyluracil 7 and N-2 isobutyryl, O-6 [2-(4-nitrophenyl)ethyl]guanine **10**,[10] to **5** (Scheme 3). The former compound was conviently prepared in a one pot sequence by treatment of 5-bromovinyluracil with benzoyl chloride and pyridine in acetonitrile for 2.5 days at room temperature. The N-3 benzoylated compound 7 precipitated out of solution and was obtained in 81% yield without the need to isolate the N-1,N-3 bis-benzoylated intermediate.[11]



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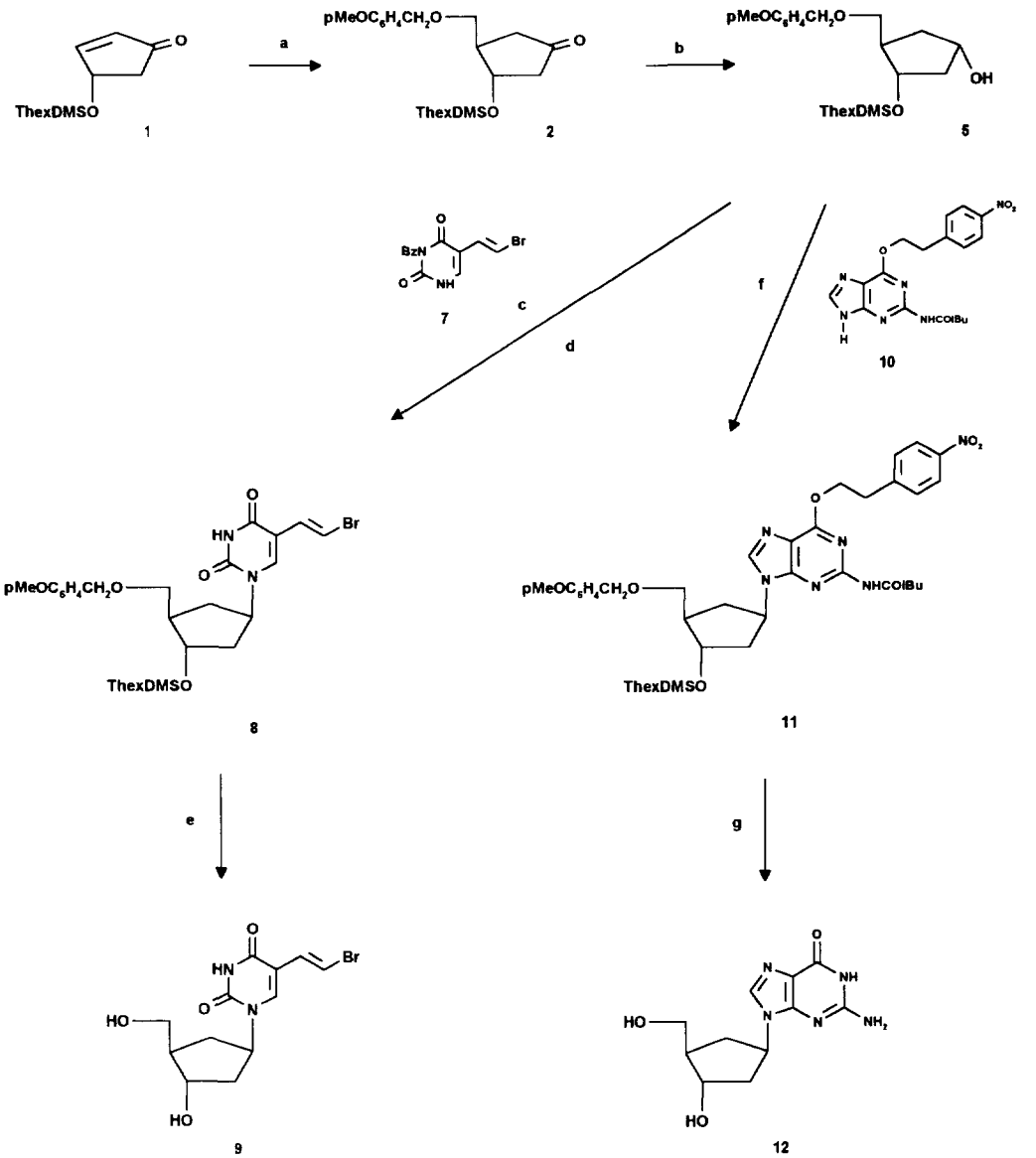
We have found that for the Mitsunobu reaction to be successful the order in which the components are added to each other is crucial. When a solution of DEAD (diethyl azodicarboxylate) in dioxane was added to a solution of the alcohol **5**, triphenylphosphine and N-3 benzoylated 5-bromovinyl uracil **7** in dioxane and DMF (3:2), an approximately 2:1 mixture of the N- and O- alkylated products[12] was obtained in 69% yield. Debenzoylation of the mixture with ammonia in methanol followed by chromatographic purification gave **8** in 36% yield (Scheme 3). Removal of the protecting groups from **8** with trifluoroacetic acid gave (+) carbocyclic 2'-deoxy-5-[(E)-2-bromovinyl] uridine (+ C-BVDU) **9** in 56% yield. Coupling the protected purine **10**[10] with

alcohol **5** under the same conditions gave the N-2 isobutyryl, O-6 [2-(4-nitrophenyl)ethyl]guanine derivative **11** in 63% yield, which was deprotected using base (DBU/py, then ammonia in methanol) followed by trifluoroacetic acid to give (+) carbocyclic 2'-deoxyguanosine (+ C-DG) **12** in 28% yield (Scheme 3).

Scheme 3



Reagents and conditions: (a) (2-Th)(PMBOCH$_2$)CuCNLi$_2$ / TMSCl, THF, -78°. (b) *Mucor circinelloides*, pH 8, 25°. (c) **7**, Ph_3P, DMF / dioxane, $EtO_2CN{=}NCO_2Et$. (d) NH_3 / MeOH. (e) TFA, 20°. (f) **10**, Ph_3P, dioxane / DMF, then add $EtO_2CN{=}NCO_2Et$, / dioxane, RT. (g) DBU/py; NH_3 / MeOH; TFA.

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8. **Method:** Typically, *M. circinelloides* was grown at 25°C on a media containing mycological peptone, 20g; yeast extract, 5g; malt extract, 5g; glucose, 20g; pH 5.5 for one day. This was used to inoculate a seed flask (50ml) and grown for a further 2 days. A series of larger flasks containing 200ml of the medium were subsequently inoculated (1-2% v/v). **2** was added at 5g/ L at the second day and incubated for up to 27 days. The culture broth was then extracted with an equal volume of neat acetonitrile. Cells were removed by filtration, the resulting supernatants were combined and **5** was isolated by preparative HPLC (Spherisorb ODS2 column, 80% acetonitrile : 20% 50mM $NH_4H_2PO_4$(v/v)).

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