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Synthesis of (±) *cis*-substituted cyclohexenyl and cyclohexanyl nucleosides via a double Mitsunobu-type reaction

Karine Barral,[a] Philippe Halfon,[b] Gérard Pèpe[a] and Michel Camplo[a,*]

[a]*Groupe de Chimie Organique et des Matériaux Moléculaires (UMR-CNRS 6114), Faculté des Sciences de Luminy, case 901, F-288 Marseille cedex 09, France*
[b]*GenoScience, Marseille, France*

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Abstract—This letter describes the synthesis of (±) *cis*-substituted cyclohexenyl and cyclohexanyl nucleosides. The synthesis of *cis* isomers was successfully achieved by the use of two consecutive Mitsunobu reactions involving an inversion of configuration and a sugar–base condensation.

The development of new modified nucleosides as antiviral agents has remained a very active field of research. Despite the fact that the carbocyclic nucleosides have been extensively studied, few efforts have been directed toward the synthesis of six-membered carbocyclic analogues.[1] However, two recent publications describe the potent antiviral activity of such compounds.[2]

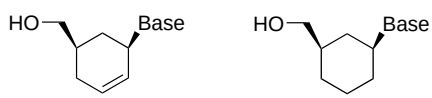
The major reasons which highlight the importance of six-membered carbocyclic nucleosides are:

– the protection from resistance to hydrolysis since glycosidic bond cleavage is a frequently encountered degradative pathway of nucleoside antivirals, particularly for the 2′,3′-dideoxynucleosides;[3]
– the cyclohexene ring on nucleosides has been shown to be a (bio)isostere of the saturated furanose ring.[4]

In this article, we describe the syntheses of several (±) *cis*-substituted cyclohexenyl and cyclohexanyl nucleosides (**I** and **II**, Fig. 1), starting from the commercially available precursor **1** (racemic 3-cyclohexene-1-carboxylic acid). The known allylic alcohol derivative **7** (Scheme 1) is a requisite for the Mitsunobu coupling reaction of various nucleoside bases.[5] Iodolactonization, followed by elimination of the iodide **2** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), afforded the unsaturated lactone **3** in quantitative yield.[6] Reduction of **3** with lithium aluminium hydride, followed by the selective protection of the primary alcohol function of the analogue **4**, provided **5** in 58% yield from compound **3**. The preparation of the *trans* derivative **6** was accomplished using a Mitsunobu-type reaction on the allylic alcohol **5**. Thus, the introduction of a benzoyl protective group allowed an inversion of configuration.[7] The allylic alcohol **5** was reacted with benzoic acid in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) in dry THF to give **6**. Alkaline hydrolysis of **6** afforded in 93% yield the *trans* allylic alcohol **7**.[8]

The corresponding *cis*-cyclohexenyl nucleosides were obtained by the use of a second Mitsunobu-type reaction between the allylic alcohol **7** and pyrimidine and purine bases.[9] The synthesis of the cytosin-1-yl (**10**), thymin-1-yl (**13**), adenin-9-yl (**17**) and guanin-9-yl (**19**) derivatives are illustrated in Schemes 2 and 3.

Condensation of the common intermediate, allylic alcohol **7**, respectively, with N^4-benzoylcytosine and N^3-benzoylthymine[10] in the presence of DEAD and triphenylphosphine in THF gave the *cis* racemic cytosine and thymine derivatives **8** and **11** in 55 and



(±)-*cis* **I** (±)-*cis* **II**

Base : cytosin-1-yl (**I**, **II**); thymin-1-yl (**I**, **II**); adenin-9-yl (**I**, **II**); guanin-9-yl (**I** only)

Figure 1.

Keywords: cyclohexenyl and cyclohexanyl nucleosides; carbocyclic nucleosides; Mitsunobu reaction.

* Corresponding author. Tel.: 33 (0)4 91 82 95 86; fax: 33 (0)4 91 82 95 82; e-mail: camplo@luminy.univ-mrs.fr

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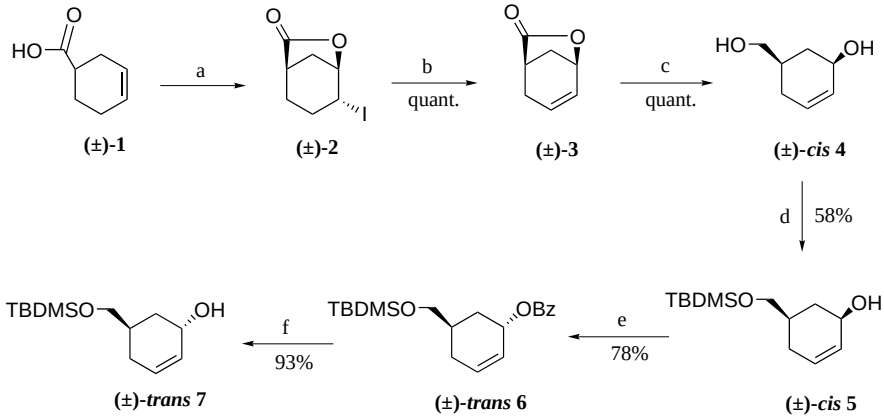
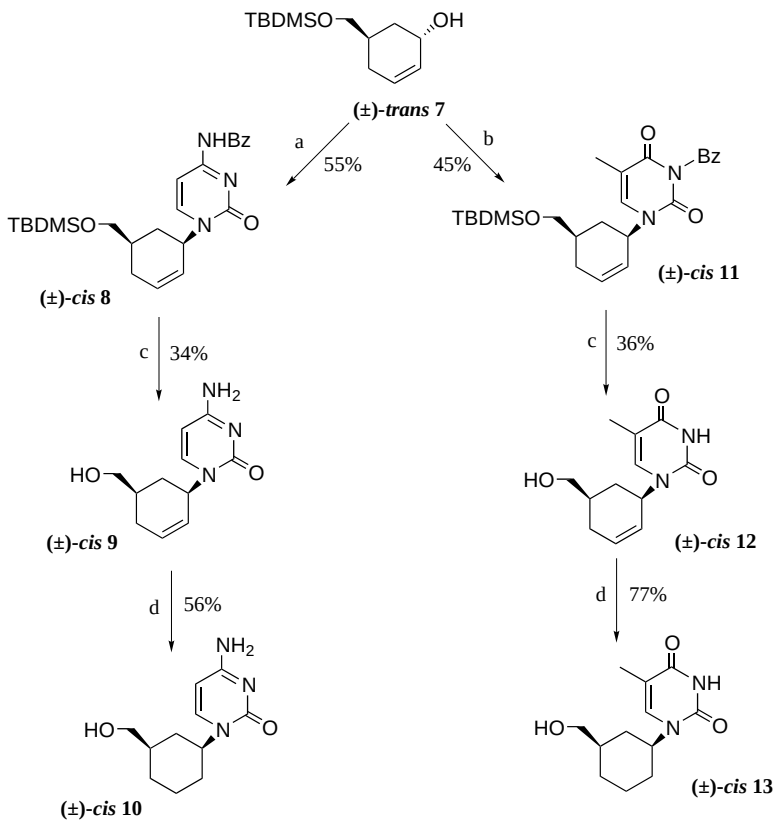


Scheme 1. *Reagents and conditions*: (a) Aq. $NaHCO_3$, then aq. KI/I_2; (b) DBU, toluene, reflux, 10 h; (c) $AlLiH_4$, THF, rt, 2 h; (d) TBDMSCl, imidazole, DMF, rt, 5 h; (e) DEAD, PPh_3, BzOH, THF, rt, 5 h; (f) NH_3/MeOH, NaOH 2N, rt, 3 h.

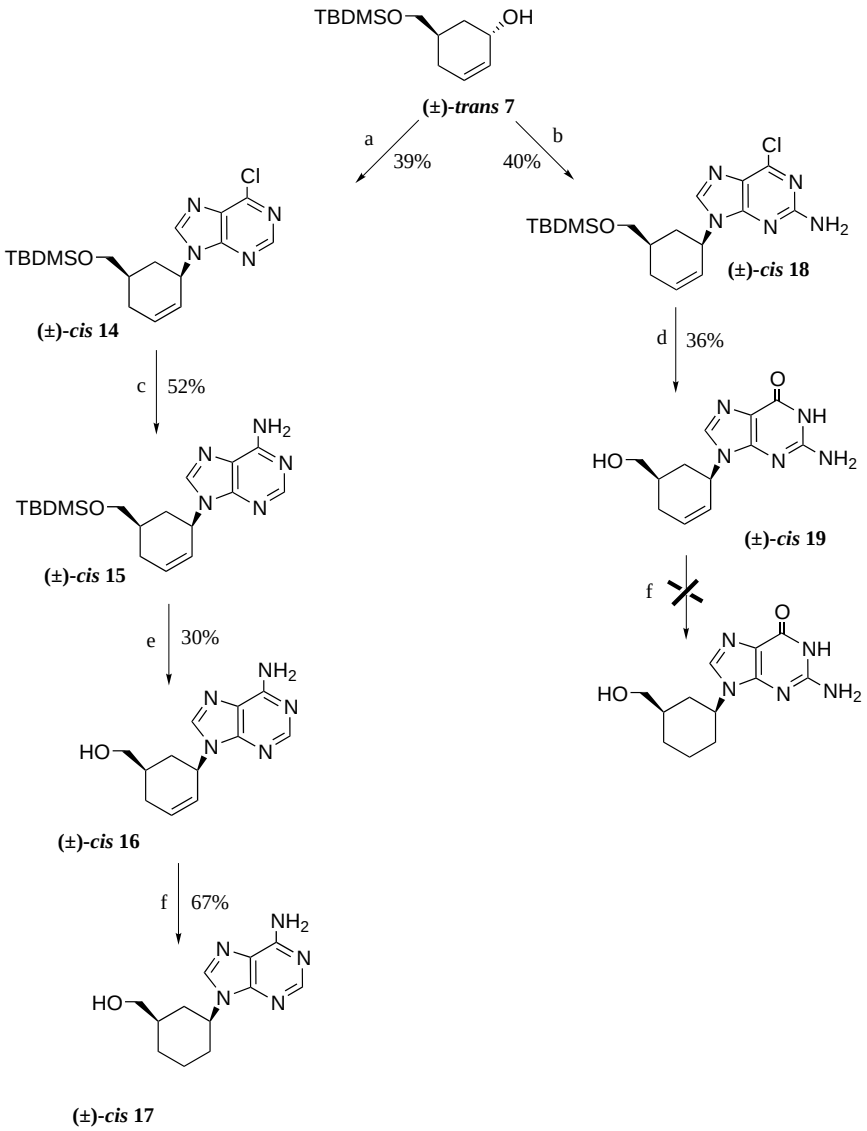
45% yield (Scheme 2).[11] Compounds **8** and **11** were converted to compounds **9** and **12** by treatment with TBAF in THF followed by a saturated ammonia solution in MeOH. The overall yields starting from **8** and **11** were 34 and 36%, respectively. Hydrogenation of compounds **9** and **12** in EtOAc over 10% palladium on carbon gave the saturated cytosine derivative **10** and the saturated thymine derivative **13** in 56 and 77% yield, respectively.[12,13]

Using the same conditions, the Mitsunobu-type reaction on the allylic alcohol **7** with 6-chloropurine and 2-amino-6-chloropurine gave the protected 6-chloropurines derivatives **14** and **18** in 39 and 40% yield, respectively (Scheme 3).[14]

Building of the adenine ring from **14** was accomplished by treatment with methanolic ammonia in a sealed reaction vessel for 1 day to give **15** in 52% yield. The material was converted to pure adenine cyclohexene nucleoside **16** by treatment with TBAF in THF. The 2-amino-6-chloropurine derivative **18** was converted to the guanine cyclohexene nucleoside **19** by treatment with TFA–H_2O (3:1). Under these conditions, the



Scheme 2. *Reagents and conditions*: (a) N^4-Benzoylcytosine, DEAD, PPh_3, THF rt, 18 h; (b) N^3-benzoylthymine, DEAD, PPh_3, THF, rt, 18 h; (c) TBAF, THF, 3 h, then satd NH_3/MeOH, 20 h; (d) 10% Pd/C, H_2, EtOAc, 24 h.



Scheme 3. *Reagents and conditions*: (a) 6-Chloropurine, DEAD, PPh_3, THF, rt, 18 h; (b) 2-amino-6-chloropurine, DEAD, PPh_3, dioxane, rt, 48 h; (c) NH_3/MeOH, 80°C, 24 h; (d) TFA/H_2O (3/1), rt, 72 h; (e) TBAF, THF, 4 h; (f) 10% Pd/C, H_2, EtOH, rt, 24 h.

TBDMS protecting group was simultaneously removed with an overall yield of 36%. Hydrogenation of compound **16** over palladium on activated carbon gave the saturated adenine derivative **17** in 67% yield. However, hydrogenation in MeOH of compound **19** led to decomposition and the use of EtOAc was inappropriate since **19** was unsoluble in this solvent. Structural assignments of the products **9**, **10**, **12**, **13**, **16**, **17** and **19** were based on 1D and 2D ^1H–^1H NMR studies. Ring conformation and relative stereochemistry of the base and the 3′-hydroxymethyl group were determined by examination of 2D ^1H–^1H NOESY spectra. In all cases, strong NOE interactions were observed between H1′, H2′ and H3′ suggesting the *cis* configuration ($H1'_{ax}$–$H3'_{ax}$) of the nucleosides (Fig. 2).

Antiviral activity of these new series of nucleosides will be reported in due course.

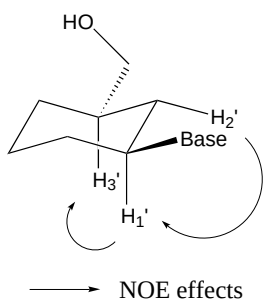


Figure 2.

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