The preparation of Carbocyclic DDIU (2',3'-DiDeoxy IodoUridine) *via* electrophilic iodination and biological study.

[a] Gwangil An, [b] Tae Hyun Choi, [b] Myung Jin Lee, a Hyun Seok Ahn, [b] Chang Woon Choi, [b] Sang Moo Lim, a Kwon Soo Chun, c HakJune Rhee.

a Radiopharmaceuticals *Laboratory, Korea Institute of Radiological and Medical Sciences (KIRAMS), Gongleung-Dong 215-4, Nowon-Gu, Seoul, 139-706, gwangil@kcch.re.kr*

b Lab. Of Nuclear Medicines, , *Korea Institute of Radiological and Medical Sciences (KIRAMS), Gongleung-Dong 215-4, Nowon-Gu, Seoul, 139-706*

c. *Dept. of Chemistry, Hanyang University, 1271 Sa-1 dong, Sangnok-gu, Ansan, Kyeonggi-do, 425-791.*

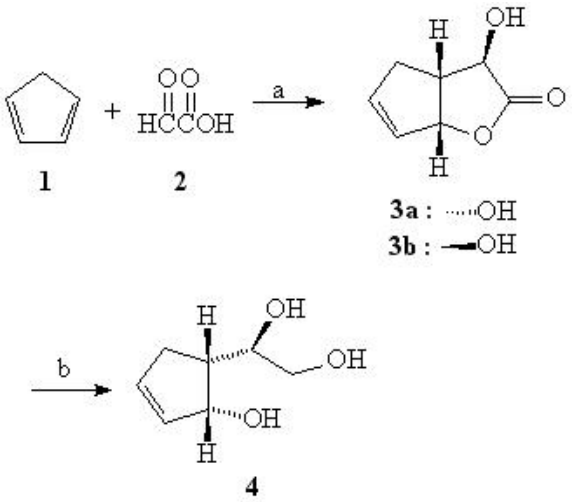
1. Introduction

Interest in the synthesis of carbocyclic nucleosides and carbocyclic analogues of normal nucleosides has grown exclusively since the potential antiviral and antitumor therapeutic agents. The replacement of the furanose oxygen by a carbon gives the nucleoside increased *in vivo* stability. Radioiodinated carobcyclic DDIU was evaluated for monitoring of HSV1-TK (herpes simplex virus type 1 thymidine kinase) gene transduced MCA hepatoma cells and wild-type MCA cells.

In this study, we whis to report here an efficient synthetic route for carbocyclic radiopharmaceuticals starting from cyclopentadiene

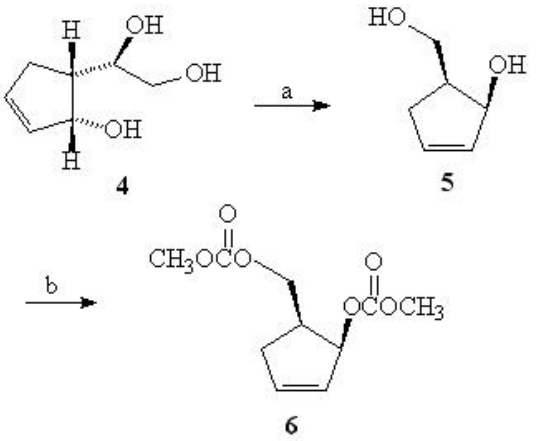
2. Methods and Results

Hetero Diels-Alder reaction of cyclopentadiene(**1**) and glyoxylic acid(**2**) in water was known as a facile method for the synthesis of bicyclic α-hydroxy-γ-lactone **3** (Sch. 1)[1].



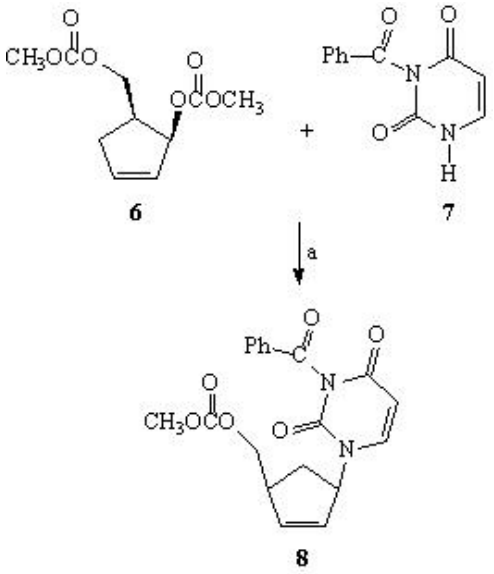
Scheme 1. **a**: Toluene, H_2O, rt, 24h, 79 % **b**: $LiAlH_4$, THF, reflux, 2h, 96 %

The products of this reaction were able to be separated by silica-gel column chromatography (**3a** : **3b** = 1.72 : 1), however, we used mixture in next step without separation. Hydroxylactone **3** can be converted to the triol **4** by lithium aluminum hydride reduction (Sch. 1) Cleavage of the vicinal diol moiety of triol 4 with sodium periodate followed by sodium borohydride reduction gave a diol **5**. Treatment of diol **5** with methyl chloroformate and 4-dimethylaminopyridine (DMAP) in pyridine afforded the dicarbonate **6** (Sch 2).



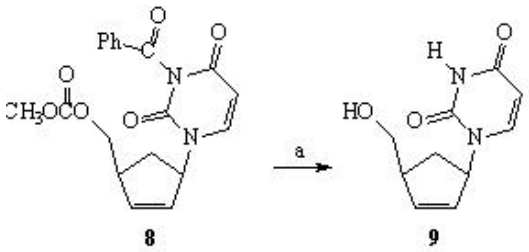
Scheme 2. **a**: i)$NaIO_4$, diethyl ether/H_2O, 2h. ii) ethylene glycol, 1h, iii) $NaBH_4$, 2h, 70 %. **b**. methyl chloroformate, DMAP (cat.), pyridine, 30 min, 93 %

The dicarbonate **6** was then subjected to the Pd(0)-catalyzed coupling reaction with 3-benzoyl uracil **7** gave coupling adduct **8** in 94 % yield (Sch 3).
3-Benzoyl uracil **7** was prepared by Known procedure in good yield[2].



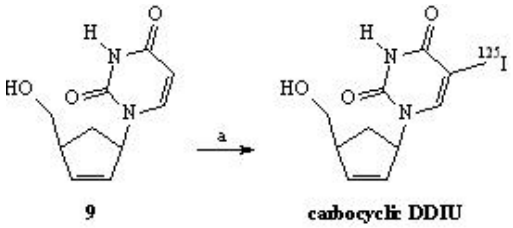
Scheme 3. **a**: i)$Pd(OAc)_2$, (i-$PrO)_3P$, THF, rt ii) n-BuLi, rt iii) **6** in THF iv) **7** in DMSO, 3h, 94 %

The coupling adduct **8** was separated in 94 % yield, and hydrolysis of the compound **8** with 0.5 M aqueous potassium carbonate solution in room temperature gave a desired precursor **9** for radioiodination (Sch 4).



Scheme 4. **a**: 0.5 M K_2CO_3 in H_2O, 24 h, 84 %

The synthetic route employed cyclopentadiene **1** as a starting material and proceed in good yield through 8 steps which contain Pd(0)-catalyzed coupling reaction and radioiodination as key reactions.
Carbocyclic DDIU was radioiodinated with I-125 by mixing with Icl by using compound **9** (Sch 5).
This radioiodinated compound was purified with reverse phase HPLC system. Cellular uptake of radiocarbocyclic DDIU was determined at fixed MCA and MCA-TK cell density for 12 hr incubation.



Scheme 5. **a**: ICl, $Na^{125}I$

The synthesis of precursor for iodination was achieved from cyclopentadiene in 37 % overall yield and iodination was employed in high yield.
Specific radioactivity of radiocarbocyclic DDIU was approximately $6x10^{-5}$ mCi/mg. The MCA-TK uptake of radiocarbocyclic DDIU was about 2 times higher than MCA uptake at 12 hr incubation.

3. Conclusion

The synthesis of carrier free carbocyclic DDIU is currently under investigation. We hope this synthetic protocol can be a useful method for the synthesis of other carbocyclic radiopharmaceuticals. These results suggest that radioiodinated carbocyclic DDIU can be applied to monitoring of HSV1-TK gene expression.

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2. Kenneth, A. C.; Josef, J.; Colin, B. R. Tetrahedron Letters. **1984**, *25(6)*, 681-684.