The preparation of 1-[4′-(hydroxymethyl)-cyclopent-2′-enyl]-5-iodouracil(Carbocyclic DDIU) *via* electrophilic iodination and its biological study.

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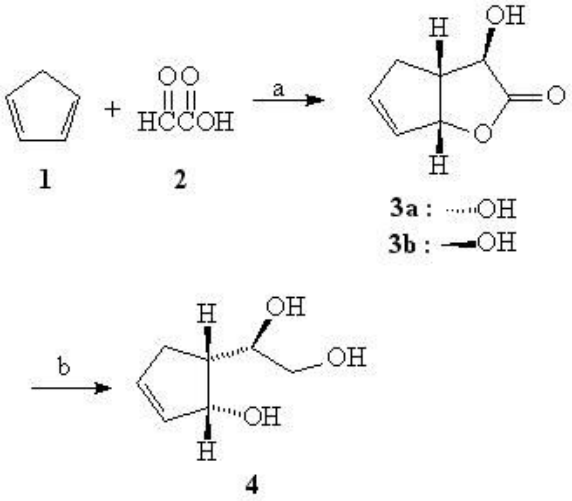
1. Introduction

The study for a number of 5-iododeoxyuridine analogues has been exclusively since the potential antiviral and antitumor therapeutic agents. The major goal of those studies was to prepare the more suitable radioiodine-labeled nucleoside analogues are effective and stable *in vivo* biodistribution as well as *in vitro* test.

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

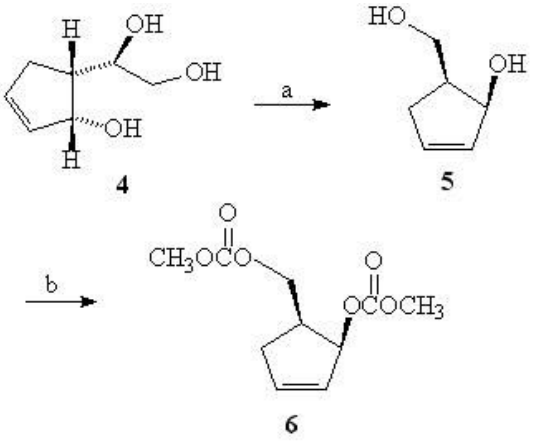
2. Methods and Results

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].



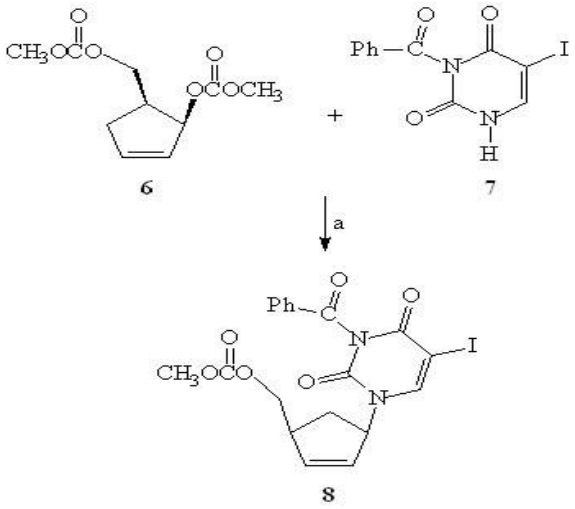
Scheme 1. **a**: Toluene, H_2O, rt, 24h, 79 % **b**: $LiAlH_4$, THF, reflux, 2h, 96 %

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).



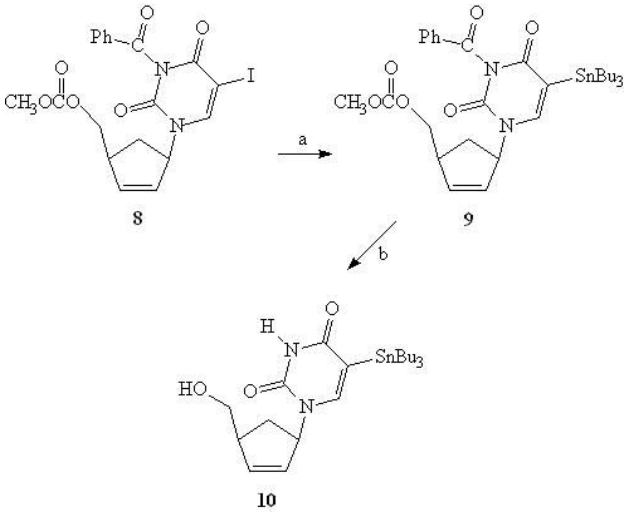
Scheme 2. **a**: i)$NaIO_4$, diethyl ether/H_2O, 2h. ii) ethylene glycol, 1h, iii) $NaBH_4$, 2h, 70 %. **b**. methyl chloroformate, DMAP (cat.), pyridine, 30 min, 93 %

3-Benzoyl 5-iodouracil **7** which is coupling partner with dicarbonate **6** was prepared from 5-iodouracil by Known procedure in good yield[2].
The coupling reaction of dicarbonate **6** was then effected by 3-*N*-benzoyl 5-iodouracil **7** in THF-DMSO(1:1) mixed solution in the presence of 5 mol % tetrakis(isopropyl phosphite)palladium(0)-catalyst. The coupling product **8** was separated in 93 % yield by the silica gel column chromatography. (Sch 3).



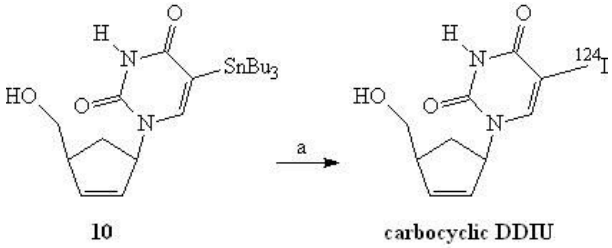
Scheme 3. **a**: i)Pd(OAc)$_2$, (*i*-PrO)$_3$P, THF, rt ii) *n*-BuLi, rt iii) **6** in THF iv) **7** in DMSO, 3h, 94 %

Then, we introduced tributylstannyl group as a leaving group at the 5-position of the compound **8** and hydrolysis of the compound **9** with 0.5 *M* aqueous potassium carbonate solution in room temperature gave a desired tin precursor **10** for radioiodination (Sch 4).



Scheme 4. **a**. i) Pd(PPh$_3$)$_4$(cat.), 1,4-dioxane.
ii) bis(tributyltin), reflux, 7 h, 73 %.
b: 0.5 *M* aqueous K_2CO_3, 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-124 by using compound **10** (Sch 5). This radioiodinated compound was purified with reverse phase HPLC system (fig.1).



Scheme 5. **a**: H_2O_2, Na^{124}I

Purification of the radioiodinated product was performed by HPLC separation on a μBondapak C 18 10 mm column (3.9 mm x 300 mm) and eluted at a flow rate of 2.0 mL/min with 0.1% TEA contained water/EtOH (retention time of the product: 15.725 min).

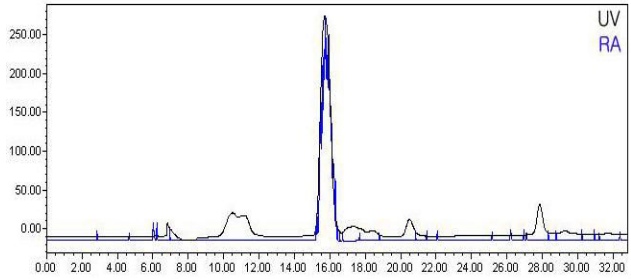


Fig. 1. HPLC analysis for radiolabeled 1-[4′-(hydroxyl methyl)-cyclopent-2′-enyl]-5-[^{124}I]iodouracil (RA) with reference material (UV).

The synthesis of tin precursor for radioiodination was achieved from cyclopentadiene in 37 % overall yield and radioiodination 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 20-60 folds higher than MCA uptake at 12 hr incubation.

3. Conclusion

The biological study by using 1-[4′-(hydroxymethyl)-cyclopent-2′-enyl]-5-[^{124}I]iodouracil 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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