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A New Entry to Carbocyclic Nucleosides: Oxidative Coupling Reaction of Cycloalkenylsilanes with a Nucleobase Mediated by Hypervalent Iodine Reagent

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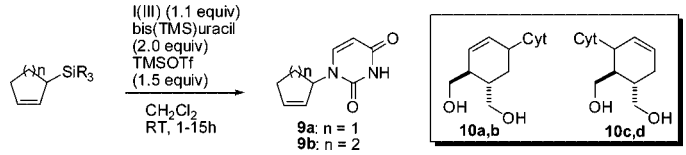
ABSTRACT



A novel method for synthesizing carbocyclic nucleosides was developed. The new synthesis includes a direct coupling reaction of cycloalkenylsilanes with a silylated nucleobase catalyzed by a hypervalent iodine reagent. By applying the method, a novel carbocyclic cytidine derivative having bis(hydroxymethyl)cyclohexene as a pseudosugar moiety, designed as a potential anti-HIV agent, was successfully synthesized.

Carbocyclic nucleosides are a unique class of nucleosides in which ring oxygen atoms of sugars are replaced with methylene groups. One of the most attractive characteristics of carbocyclic nucleosides is their antiviral activities.[1–4] Since the discovery of the potent antihuman immunodeficiency virus (HIV) activity of carbovir **1**,[1] a cyclopentene ring has been recognized as a ribofuranose equivalent for designing new anti-HIV nucleosides. For instance, cyclopentenylcytosine **2**[2] and bis[(hydroxymethyl)cyclopentenyl]adenine (BCA) **3**[3] were shown to possess anti-HIV activities. A cyclohexenyl nucleoside, a homologue of cyclopentenyl nucleosides, is also interesting: cyclohexenylguanine **4** is known to have anti-human herpes simplex virus type 1 (HSV-1) activity.[4]

As one part of our continuous study to search for new anti-HIV agent,[5] the synthesis of a novel cycloalkenyl nucleoside was envisioned. The direct introduction of a

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(1) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17.
(2) Song, G. Y.; Paul, V.; Choo, H.; Morrey, J.; Sidwell, R. W.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2001**, *44*, 3985.
(3) Katagiri, N.; Shiraishi, T.; Sato, H.; Toyota, A.; Kaneko, C.; Yusa, K.; Oh-hara, T.; Tsuruno, T. *Biochem. Biophys. Res. Commun.* **1992**, *184*, 154.
(4) Wang, J.; Froeyen, M.; Hendrix, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **2000**, *43*, 736.
(5) (a) Yamada, K.; Sakata, S.; Yoshimura, Y. *J. Org. Chem.* **1998**, *63*, 6891. (b) Yoshimura, Y.; Asami, K.; Matsui, H.; Tanaka, H.; Takahata, H. *Org. Lett.* **2006**, *8*, 6015. (c) Yoshimura, Y.; Yamazaki, Y.; Kawahata, M.; Yamaguchi, K.; Takahata, H. *Tetrahedron Lett.* **2007**, *48*, 4519.
(6) Typically, Mitsunobu reaction and Pd-catalyzed cross-coupling reaction have been used:(a) Barral, K.; Halfon, P.; Pèpe, G.; Camplo, M. *Tetrahedron Lett.* **2002**, *43*, 81. (b) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745.

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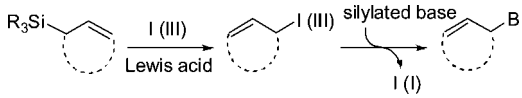
nucleobase to a precursor for pseudosugar is the most straightforward access to the target carbocyclic nucleosides.[6]

We decided to explore a new oxidative coupling reaction of cyclic allylsilane with a persilylated nucleobase that could be applied to the synthesis of cycloalkenyl nucleosides. For that, reaction using a hypervalent iodine reagent[7] was tried (Scheme 1). To our knowledge, there has been only one

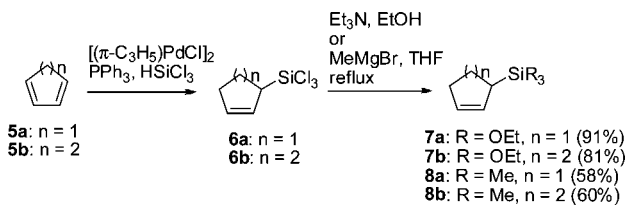
Scheme 1. New Access for Carbocyclic Nucleosides



report on a C−N bond formation by a hypervalent iodine reagent.[7b]

First, an oxidative coupling reaction was examined by a model reaction using simple cycloalkenylsilanes. Cyclopent-2-enylsilanes **7a**, **8a** and cyclohex-2-enylsilanes **7b**, **8b** were prepared by hydrosilylation[8] of cyclopentadiene and cyclohexadiene, respectively (Scheme 2). Along with our initial

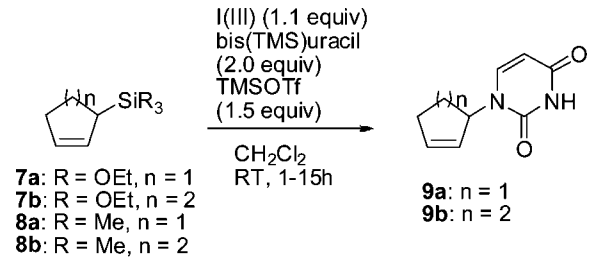
Scheme 2. Synthesis of Cycloalkenylsilane



plan, the coupling reaction of **7** and **8** with persilylated uracil in the presence of a hypervalent iodine reagent and TMSOTf was examined (Scheme 3). The results are summarized in Table 1.

To our delight, the reactions of allylsilanes **7a** and **7b** with persilylated uracil in the presence of (diacetoxyiodo)benzene gave cycloalkenyluracils **9a** and **9b** in 45% and 49% yields, respectively (entries 1 and 2). Because of the slow reaction and the formation of side products, the use of triethoxysilanes was abandoned, and reactions using trimethylsilyl derivatives were next examined. Treatment of allyltrimethylsilanes **8a** and **8b** under the same conditions as those described above gave **9a** and **9b** in 65% yield (entries 3 and 4). Oxidative coupling reactions of **8b** with various hypervalent iodine reagents were also attempted. The use of [di(trifluoroacetoxy)iodo]benzene and iodosobenzene slightly diminished the reaction yields (entries 5 and 6). On the other hand, the

Scheme 3. Oxidative Coupling Reaction of Cycloalkenylsilane with Uracil



reaction using [hydroxyl(tosyloxy)iodo]benzene gave **9b** in a poor yield (entry 7).

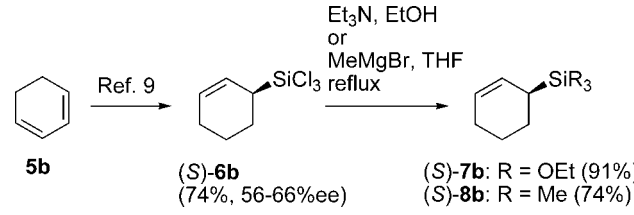
Table 1. Summary of the Oxidative Coupling Reaction of Cycloalkenylsilane and Uracil

entry	silane	I(III)	time (h)	yield (%)
1	**7a**	$PhI(OAc)_2$	15	45
2	**7b**	$PhI(OAc)_2$	15	49
3	**8a**	$PhI(OAc)_2$	1	65
4	**8b**	$PhI(OAc)_2$	1	65
5	**8b**	$PhI(O_2CCF_3)_2$	1	55
6	**8b**	PhIO	1	57
7	**8b**	PhI(OH)OTs	1	29

As considered from the chemistry of hypervalent iodine, the coupling reaction should proceed via an allyl cation generated by the reaction of (diacetoxyiodo)benzene and allylsilane. To prove the reaction mechanism, we envisaged performing the oxidative coupling reaction using chiral alkenylsilane.

Enantioselective hydrosilylation of **5b** using chiral (*R*)-Ar-MOP ligand, which has been developed by Hayashi and Uozumi,[9] gave (*S*)-**6b** in 74% yield with 56−66% ee. Compound (*S*)-**6b** was converted to (*S*)-**7b** and (*S*)-**8b** as described above (Scheme 4).

Scheme 4. Enantioselective Synthesis of Chiral Cyclohexenylsilanes



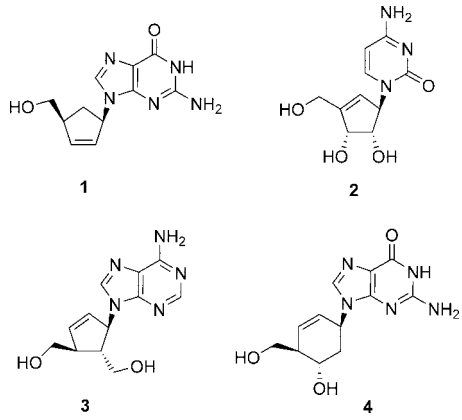
The oxidative coupling reaction of both (*S*)-**7b** and (*S*)-**8b** gave a racemic mixture of cyclohexenyluracil **9b** as

(7) (a) Ochiai, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *Chem. Pharm. Bull.* **1985**, *33*, 41. (b) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224. (c) Dohi, T.; Morimoto, K.; Takenaga, N.; Goto, A.; Maruyama, A.; Kiyono, Y.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 109.

(8) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099.

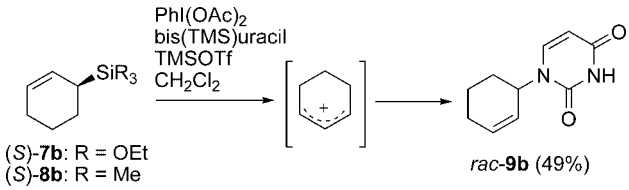
(9) Hayashi, T.; Han, J. W.; Takeda, A.; Tang, J.; Nohmi, K.; Mukaide, K.; Tsuji, H.; Uozumi, Y. *Adv. Synth. Catal.* **2001**, *343*, 279.

Chart 1



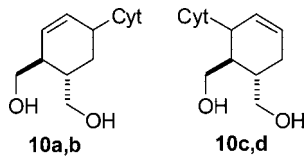
anticipated. This result strongly supports the formation of the ally cation intermediate that we presumed (Scheme 5).

Scheme 5. Oxidative Coupling Reaction Using Chiral Cyclohexenylsilane



We next focused on the application of the oxidative coupling reaction to the synthesis of new carbocyclic nucleoside derivatives designed as potential anti-HIV agents. The target molecule we selected was carbocyclic cytidines **10a**−**d** constructed on a cyclohexenyl scaffold as depicted in Chart 2.[10] Diels−Alder reaction would be suitable for

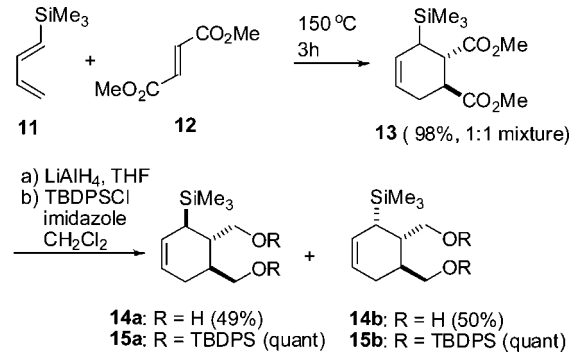
Chart 2



preparing the substrate of oxidative coupling, which would lead to **10a**−**d**, since installation of a trimethylsilyl group and stereoselective introduction of *trans*-dihydroxymethyl groups could be achieved in a single step.

(10) The synthesis of the purine derivatives of **10a** has been reported: Rosenquist, Å; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1996**, *61*, 6382. Although those were reported to be inactive against HIV, the anti-HIV activitiy of the pyrimidine derivatives has not been investigated. Additionally, **10c,d** were considered to be a new class of carbocyclic nucleosides.

Scheme 6. Synthesis of Di(hydroxymethyl)trimethylsilylcyclohexene



The Diels−Alder reaction of trimethylsilylbutadiene **11** and dimethyl fumarate **12** gave cyclohexene diester **13** as a 1:1 mixture of *endo*/*exo* isomers in good yield.[11] Hydride reduction of **13** and subsequent separation by silica gel column chromatography gave 1,2-*trans*-adduct **14a** and 1,2-*syn*-adduct **14b** in 49% and 50% yields, respectively. Compounds **14a** and **14b** were protected by the silyl group to give di-TBDPS derivatives **15a** and **15b** quantitatively. The relative stereochemistry of **14a** and **14b** was determined by ^{1}H NMR after being reduced to the corresponding cycloalkane derivatives (data not shown).

The coupling reaction of **15a** and **15b** with persilylated uracil was tried by using (diacetoxyiodo)benzene as an oxidant (Scheme 7). The results are shown in Table 2. Since the reaction is considered to proceed via an allyl cation, it was anticipated that the reaction would give a mixture of stereoisomers including regioisomers. Indeed, the reaction of **15a** gave an inseparable mixture containing four stereoisomers with a ratio of 6:10:2:1.5 estimated from the ^{1}H NMR spectrum, and the reaction of **15b** gave a similar result. Cyclohexadiene **17** obtained in both cases was thought to be formed by E1 elimination of the ally cation intermediate. It was difficult to determine their structures at this stage. Thus, the structures of the products were elucidated after conversion and isolation to final products (vide infra).

It is also interesting that **15a** and **15b** showed different reactivities under the oxidative coupling reaction. Probably, some steric interaction of the substituents on the cyclohexene ring would exist, but the details are not clear yet.

To separate stereoisomers of the cyclohexenyluracils, we tried temporary N^3-benzoylation of **16a**−**d**. Treatment of **16a**−**d** with benzoyl chloride and triethylamine gave a mixture of **18a**−**d**, which was subjected to separation by silica gel column chromatography to afford **18a**, **18d**, and a mixture of **18b** and **18c**. After debenzoylation, the compounds **16a**−**d** thus obtained were treated with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) followed by

(11) Jung, M. E.; Gaede, B. *Tetrahedron* **1979**, *35*, 621.
(12) Sekine, M.; Matsuzaki, J.; Satoh, M.; Hata, T. *J. Org. Chem.* **1982**, *47*, 571.
(13) Anti-HIV-1 activities of the compounds were evaluated by suppression of HIV replication in PBMCs by p24 antigen capture assay.

Table 2. Summary of the Oxidative Coupling Reaction of **15a**/**15b** and Uracil

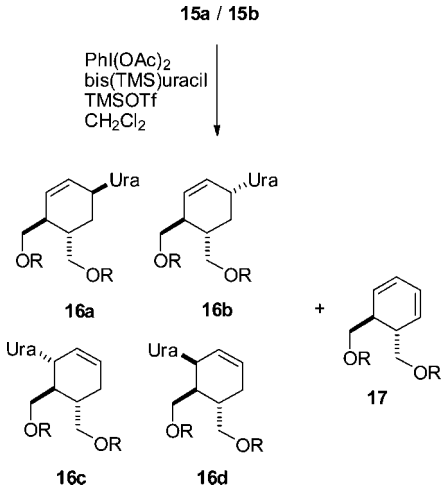
		yield (%)			ratio
compd	time (h)	**16a**−**d**	**17**	recov	**16a**:**16b**:**16c**:**16d**
15a	1	60	18	0	6:10:2.0:1.5
15b	24	50	11	20	3:10:2.5:0.5

aqueous ammonia to give cytidine derivatives **19a**−**d**.[12] At this step, all stereoisomers could be completely separated. Finally, desilylation of **19a**−**d** gave desired **10a**−**d** in good yields.

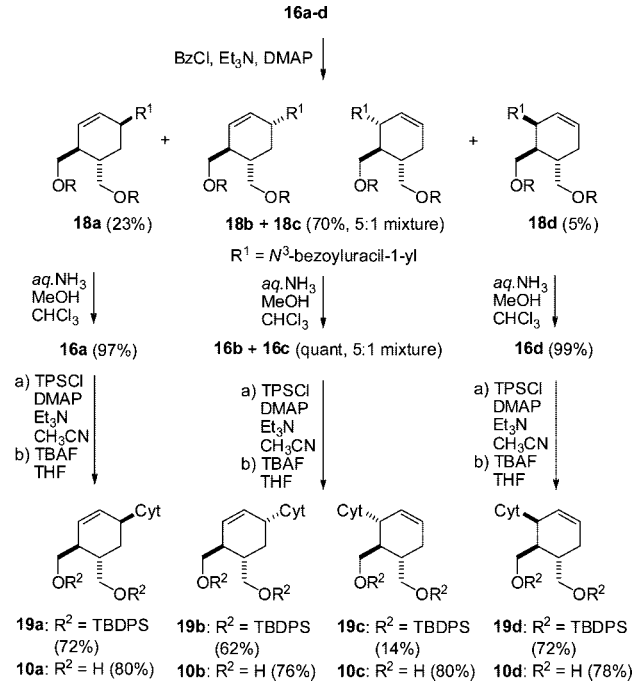
From 2D-NMR data and NOE experiments, the structures of **10b** and **10c** were determined as shown in Figure 1 in Supporting Information. As a result, the structures of **10a** and **10d** were estimated as depicted in Scheme 8. The stereochemical outcome of the oxidative coupling of allylsilane **15a/b** with uracil could be explained by steric interactions depicted in Figure 2 in Supporting Information. Nucleophilic attack to the less hindered γ-carbon from the up side in the figure that would lead to formation of **16b** would be preferable.

Anti-HIV activities of **10a**−**d** were evaluated, and it was found that only **10b** inhibited HIV replication in peripheral

Scheme 7. Oxidative Coupling Reaction of **15a**/**15b** and Uracil



Scheme 8. Synthesis of cyclohexenylcytosines **10a**−**d**



blood mononuclear cells (PBMC) with 39% inhibition at 10 μM.[13] The other three isomers were inactive against HIV-1.

In conclusion, we have developed a novel oxidative coupling reaction for synthesizing carbocyclic nucleosides based on hypervalent iodine chemistry. By applying the reaction, new carbocyclic cytidine derivatives were synthesized, and the major product was found to have anti-HIV activity. Determination of an active enantiomer is our next problem to be solved.

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Supporting Information Available: Figures 1 and 2, experimental procedures, characterization data, and NMR charts (^{1}H and ^{13}C). This material is available free of charge via the Internet at http://pubs.acs.org.

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