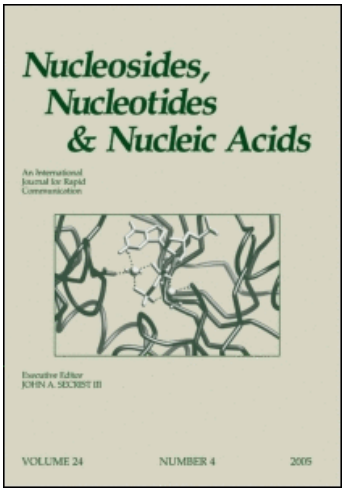

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A FACILE SYNTHESIS OF *CIS*-4-AMINO-2-CYCLOPENTENE-1-METHANOL, A KEY INTERMEDIATE FOR THE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES

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ABSTRACT

A number of carbocyclic nucleosides can be synthesized from (±)-*cis*-4-amino-2-cyclopentene-1-methanol **(3)**. Carbocyclic amino alcohol **3** is a key intermediate that makes possible the efficient synthesis of the carbocyclic nucleosides. In this study we wish to report an efficient synthesis of carbocyclic amino alcohol **3** from inexpensive and readily available starting material. The synthetic route employed cyclopentadiene **(4)** as a starting material and proceeded in 38% overall yield through 6 steps involving a hetero Diels-Alder reaction and an aza-Claisen rearrangement.

INTRODUCTION

Interest in the synthesis of carbocyclic nucleosides and carbocyclic analogues of normal purine or pyrimidine nucleosides has grown exclusively since the potential antiviral and antitumor therapeutic agents[1]. The replacement of the furanose oxygen by a carbon gives the nucleoside increased stability to the enzymes that cleave the nucleosidic bonds of the natural nucleosides in addition to modifying the biological activity[2]. Carbocyclic

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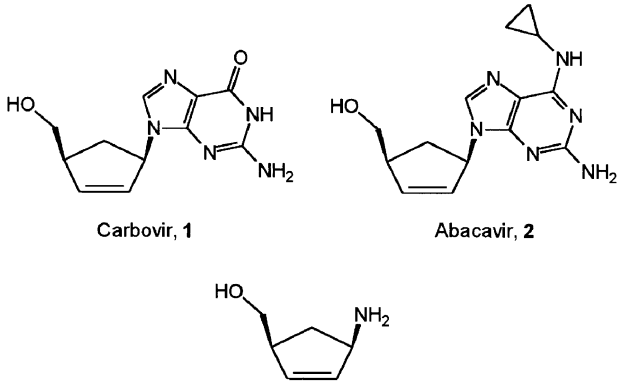
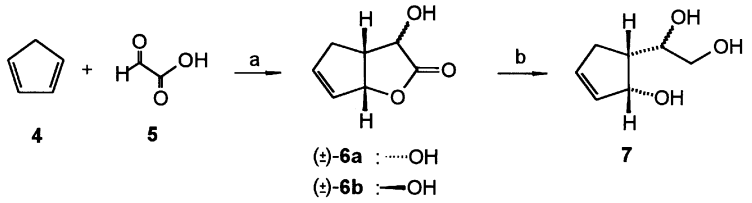
2′,3′-didehydro-2′,3′-dideoxyguanosine (carbovir, **1**)[3] was reported to be an in vitro selective inhibitor of HIV-1 and exhibited less toxicity than other agents. The analogue of (-)-carbovir, abacavir (1592U89, Ziagen, **2**), which has higher oral bioavailability than carbovir[4], is currently commercialized for the treatment of HIV infection. Two general synthetic approaches for these carbocyclic nucleosides are coupling of the intact purine to a carbocycle like cyclopentenyl derivatives and construction of the purine from the amino alcohol **3**. Among these methods, the coupling of an intact heterocyclic base to a cyclopentenyl derivative is not efficient for industrial method since palladium catalyst can be applied just for academic research works. When the palladium-catalyzed coupling reactions of nucleobase and cyclopentenyl derivatives were scaled up, the ratio of minor products is getting larger. That is a major and very serious problem for the first method, but the construction of the purine from the amino alcohol **3** is relatively suitable for a large scale. For these reasons and the important biological activity of these carbocyclic nucleosides, the synthesis of the amino alcohol, a key intermediate for carbocyclic nucleosides, increasingly important and has been focused and reported by several research groups[5]. In most cases, the amino alcohol **3** was prepared via a Diels-Alder reaction between a sulfonyl cyanide and cyclopentadiene. We wish to report here a short and an efficient synthetic route for the hydrochloride salt of carbocyclic amino alcohol **3** starting from cyclopentadiene.



Carbocyclic amino alcohol, **3**

RESULTS AND DISCUSSION

Hetero Diels-Alder reaction of cyclopentadiene **(4)** and glyoxylic acid **(5)** in water was known as a facile method for the synthesis of bicyclic α–hydroxy-γ-lactone **6** (Sch. 1)[3j,6]. The products of this reaction were able to be separated by silica-gel column chromatography (**6a**:**6b** = 1.72:1)[7],



Scheme 1. **a**. Toluene, H_2O, 40 °C, 2 h, 79% (**6a:6b** = 1.72:1). **b**. $LiAlH_4$, THF, reflux, 2 h, 96%.

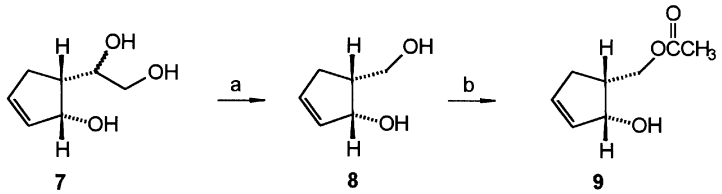
however, we used *endo*- and *exo*-hydroxylactone mixture in next step without separation. Hydroxylactone **6** can be converted to the triol **7** by lithium aluminum hydride reduction (Sch. 1)[3j,7,8].

Cleavage of the vicinal diol moiety with sodium periodate followed by sodium borohydride reduction gave a diol **8**[8]. Treatment of diol **8** with acetic anhydride in pyridine gave the acetyl mono-protected cyclopentene diol **9** (Sch. 2).

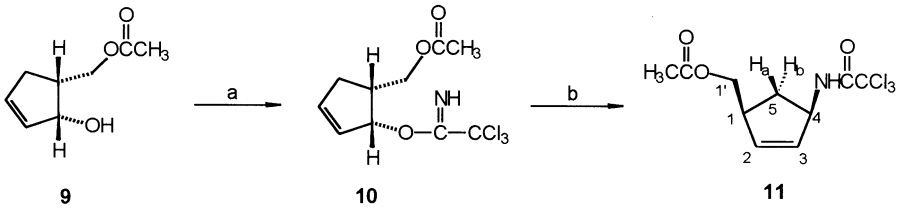
The conversion of allyl alcohol to allyl amide was achieved via 3,3-sigmatropic rearrangement, known as aza-Claisen rearrangement[9]. We applied this protocol to the allyl alcohol **9**. Thus, the reaction of allyl alcohol **9** with trichloroacetonitrile and the sequential aza-Claisen rearrangement of imidate **10** gave a desired rearranged product **11** (Sch. 3).

The compound **11** was identified by ^1H-^1H COSY spectrum (Fig. 1). In this spectrum, H4 (δ 4.78) is correlated with H3 (δ 5.87 or 5.75), H5 (δ 2.44 and 1.47: H_a and H_b), and NH (δ 9.07). Also, H1 (δ 2.95) is correlated with H2 (δ 5.87 or 5.75), H5 (δ 2.44 and 1.47: H_a and H_b), and H1′ (δ 4.01). From these data, the compound **11** was identified as a 1,4-substituted cyclopentene.

A number of problems were encountered due to the unstable nature of amino alcohol **3**[5a], especially in the hydrolysis step of the compound **11**. Because free amino alcohol **3** is unstable in light and moisture when concentrated from diluted solution, the basic hydrolysis always gave an intractable mixture. Thus, the hydrolysis of compound **11** with methanolic hydrochloric acid was attempted and afforded a stable hydrochloride salt **12** (Sch. 4).



Scheme 2. **a**. i) $NaIO_4$, diethyl ether/H_2O, 2 h. ii) ethylene glycol, 1 h. iii) $NaBH_4$, 2 h, 70%. **b**. pyridine, acetic anhydride, 0 °C, 1 d, 95%.



Scheme 3. **a**. DBU, trichloroacetonitrile, $CHCl_3$, 1 h. **b**. K_2CO_3, *p*-xylene, reflux, 14 h, 85%.

In summary, a facile synthesis of the compound **12** was achieved from cyclopentadiene **(4)** in 38% overall yield through 6 steps. From the result of the study, an amino alcohol **3** was provided as a valuable key intermediate for the synthesis of carbocyclic nucleosides.

EXPERIMENTAL

Proton (^{1}H) NMR spectra were obtained using a Varian Mercury 300 spectrometer (300 MHz) instrument operating in Fourier transform mode. Carbon-13 (^{13}C) NMR spectra were recorded using a Varian Mercury 300 spectrometer (75.5 MHz) instrument. Infrared spectra were recorded on Bio-Rad FTS 6000 FT-IR spectrometer. Uncorrected melting points were determined with a Gallenkamp melting point apparatus. Analytical thin layer chromatography (TLC) was conducted on E. Merck 60 F254 aluminum backed silica gel plates (0.2 mm) with a fluorescent indicator. Developed plates were visualized under UV light, with iodine staining, or by dipping in

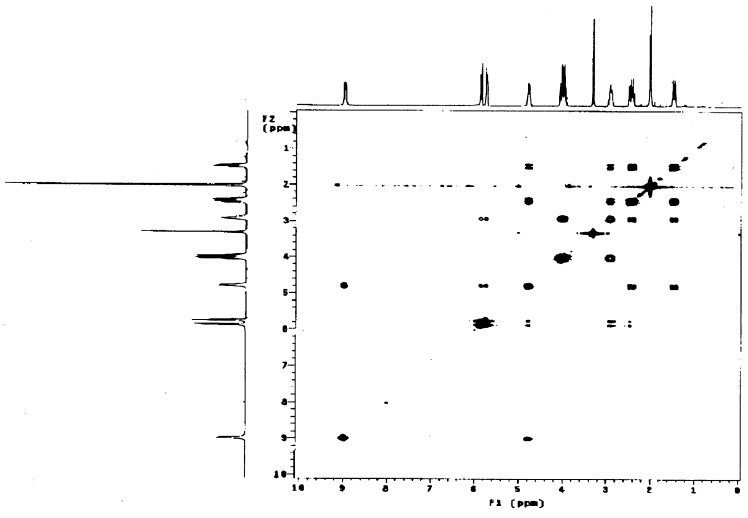
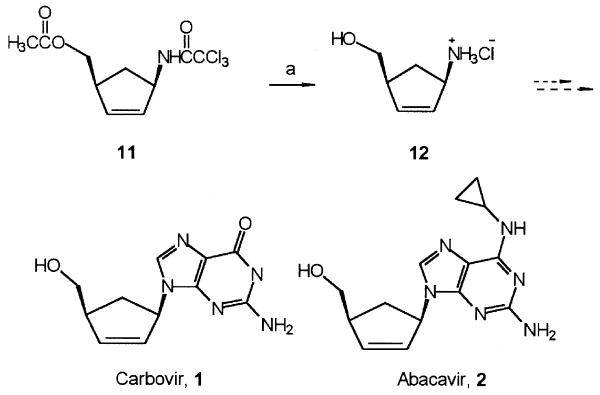


Figure 1. The ^{1}H-^{1}H COSY spectrum of compound **11**.



Scheme 4. **a.** 3 *N* methanolic HCl, reflux, 1 d, 89%.

2.0% phosphomolybdic acid solution and then heating. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh) under positive pressure of air according to the procedure of Still[10]. Reagents and solvents were of reagent grade, and solvents were purified by the known procedure before use[11].

***cis*-5-Hydroxymethyl-cyclopent-2-en-1-ol (8).** Diol **8** was prepared from triol **7** by a known procedure:[8] IR (thin film) 3423, 3058, 2930, 1615, 1441, 1350, 1155, 1019, 951, 891, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (m, 1H), 5.82 (m, 1H), 4.89 (m, 1H), 3.78 (m, 2H), 3.30 (br s, 1H), 3.06 (br s, 1H), 2.43 (m, 1H), 2.32 (m, 1H), 2.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 135.01, 132.30, 77.69, 62.69, 42.59, 33.65.

***cis*-5-Acetoxymethyl-cyclopent-2-en-1-ol (9).** To a solution of diol **8** (2.00 g, 17.5 mmol) in anhydrous pyridine (15 mL) was added acetic anhydride (1.96 mL, 19.3 mmol) in anhydrous $CHCl_3$ (7 mL) by cannulation at 0 °C. After being stirred for 1 d, the reaction mixture was diluted with $CHCl_3$ (50 mL) and washed with brine solution (50 mL × 3). The aqueous phase was extracted with $CHCl_3$ (20 mL × 3). The organic phase was collected, dried with anhydrous $MgSO_4$ and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (diethyl ether: hexane = 3:2, v/v) to give a colorless oil ($R_f = 0.25$; 2.59 g, 95%): IR (thin film) 3467, 3123, 2889, 2768, 1750, 1610, 1468, 1432, 1257, 1087, 747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.03 (m, 1H), 5.91 (m, 1H), 4.71 (m, 1H), 4.35 (m, 1H), 4.20 (m, 1H), 2.44 (m, 1H), 2.37 (m, 1H), 2.33 (br s, 1H), 2.31 (m, 1H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.29, 134.73, 132.60, 75.54, 63.85, 41.45, 33.86, 21.04; MS (EI) *m/e*: found 156 $[M]^+$, 155 $[M\text{-}H]^+$, 96 $[M\text{-}(CO_2CH_3+H)]^+$.

cis*-4-Trichloroacetamido-2-cyclopentene-1-methyl acetate (11).** To a solution of alcohol **9** (0.100 g, 0.641 mmol) in anhydrous $CHCl_3$ (7.0 mL) was added DBU (0.144 mL, 0.962 mmol) and trichloroacetonitrile (0.128 mL, 1.28 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with sat. NH_4Cl solution. The organic layer was washed with sat. NH_4Cl solution (10 mL × 2) and passed through a column packed with celite and silica gel with chloroform. The resulting solution was evaporated under reduced pressure to give crude trichloroacetimidate that used in the next reaction without any purification. The crude imidate was dissolved in anhydrous xylene (10.0 mL). Then, K_2CO_3 (0.0400 g, 0.289 mmol) was added at 0 °C to the solution. The mixture was heated at reflux temperature for 14 h with vigorous stirring. After cooling to room temperature the reaction mixture was diluted with $CHCl_3$ (15 mL) and washed with brine solution (15 mL × 3). The aqueous phase was extracted with $CHCl_3$ (20 mL × 3). The organic phase was collected, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (ethyl acetate:hexane = 1:4, v/v) to give a pale yellow gummy solid ($R_f = 0.25$; 0.163 g, 85%): IR (thin film) 3331, 3058, 2949, 2893, 1741, 1710, 1513, 1243, 1037, 834, 832 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.07 (d, ***J = 7.2 Hz, 1H), 5.87 (ddd, ***J*** = 5.4, 3.5, 0.9 Hz, 1H), 5.75 (dd, ***J*** = 4.9, 3.1 Hz, 1H), 4.78 (m, 1H), 4.01 (m, 2H), 2.95 (m, 1H), 2.44 (m, 1H), 2.02 (s, 3H), 1.47 (dd, ***J*** = 6.9, 6.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 170.15, 160.73, 133.95, 131.93, 92.81, 66.86, 57.11, 43.62, 32.89, 20.73; MS (FAB) *m/e*: calcd for ($C_{10}H_{13}Cl_3NO_3$): 299.9961, found 299.9945 $[MH]^+$.

cis*-4-Amino-2-cyclopentene-1-methanol·HCl (12)[12].** The rearranged adduct **11** (0.0400 g, 0.130 mmol) was added to 3.0 ***N methanolic HCl solution (10 mL) at −5 °C. The reaction mixture was stirred at reflux temperature for 1 d. After removal of solvent by rotary-evaporation, the residue was washed with mixed solvent (ethanol:diethyl ether = 1:50 , v/v; 25 mL). And then the residue was recrystallized to give a pale brown solid (ethanol:diethyl ether, 0.0177 g, 89%): m.p. 129–131 °C; IR (KBr) 3438, 3321, 3058, 2927, 2874, 1516, 1337, 820 cm^{-1}; ^1H NMR (D_2O) δ 6.12 (m, 1H), 5.87 (m, 1H), 4.32 (br m, 1H), 3.61 (m, 2H), 3.02 (m, 1H), 2.56 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (D_2O) δ 138.85, 127.35, 62.19, 55.47, 46.12, 30.92.

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