HETEROCYCLES, Vol.53, No.1, 2000, pp. 219 - 224, Received, 23rd August, 1999

AN EFFICIENT SYNTHESIS OF (±)-*cis*-2-AMINO-6-HYDROXY-9-[4'-HYDROXYETHYL-2'-CYCLOPENTEN-1'-YL]PURINE

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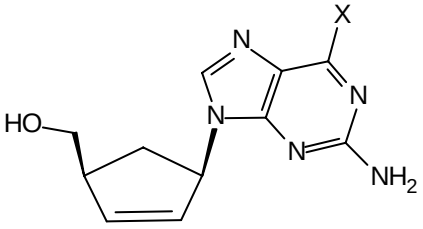
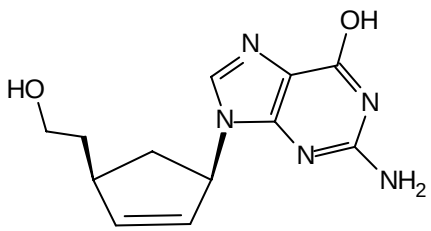
Abstract - The synthesis of a carbovir analogue, (±)-*cis*-2-amino-6-hydroxy-9-[4'-hydroxyethyl-2'-cyclopenten-1'-yl]purine (**2**) was achieved from 2,5-norbornadiene (**3**) in six steps and 31 % overall yield. This route involves a Meinwald rearrangement, one-pot operation (acid-hydrolysis and subsequent sodium borohydride reduction), and a Pd(0)-catalyzed coupling reaction.

Carbocyclic analogues of normal purine or pyrimidine nucleosides have obtained an interest as potential antiviral and antitumor agents.[1] The recently discovered carbocyclic nucleoside, (-)-carbovir (**1a**) was reported to be an *in vitro* selective inhibitor of HIV-1 and exhibited low toxicity.[2] The analogue of (-)-carbovir, abacavir (**1b**), which has higher oral bioavailability than carbovir,[3] is currently commercialized for the treatment of HIV infection. Due to the important biological activity of these carbocyclic nucleosides, our research has focused on the synthesis of carbovir analogues. We have chosen (±)-*cis*-2-amino-6-hydroxy-9-[4'-hydroxyethyl-2'-cyclopenten-1'-yl]purine [(±)-homocarbovir] (**2**) as a target compound. The synthesis of homocarbovir (**2**) has been reported by several research



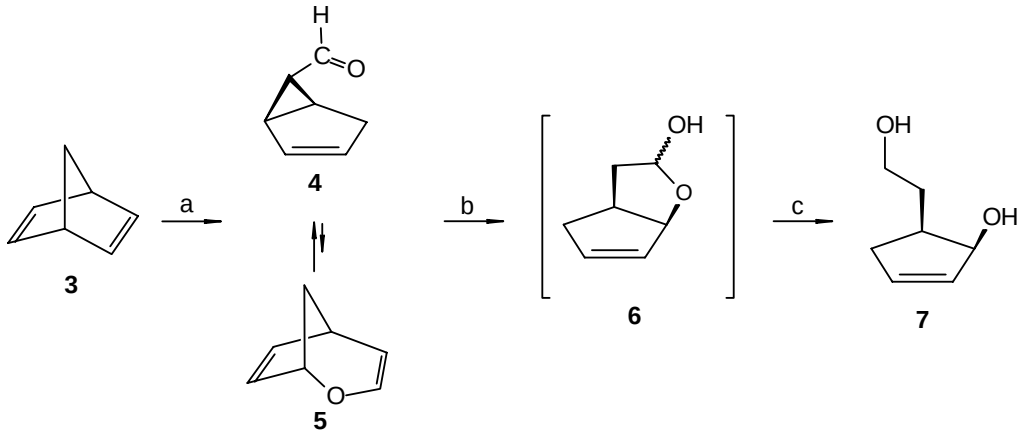
X = OH (Carbovir, **1a**)
X = NH— (Abacavir, **1b**)



(±)-Homocarbovir, **2**

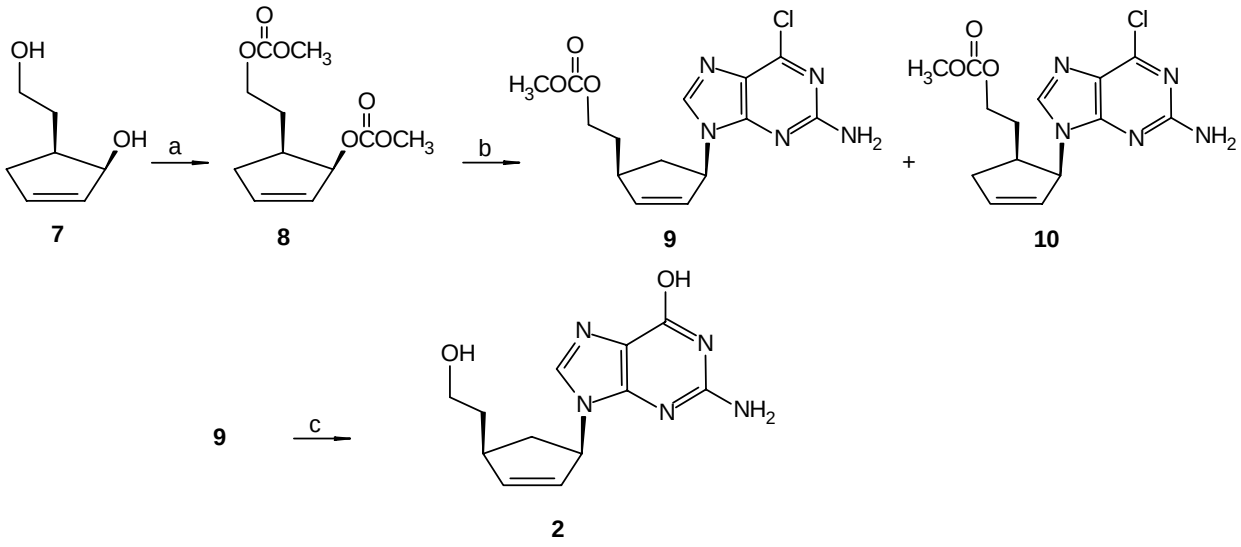
groups including us.[4] In this paper, we report a short synthetic route for the (±)-homocarbovir (**2**) starting from 2,5-norbornadiene (**3**).

Meinwald rearrangement of the peracid oxidation of 2,5-norbornadiene (**3**) gave an equilibrium mixture (ratio 7:3) of the bicyclic aldehyde (**4**) and the bicyclic enol ether (**5**).[5] A mild acid-catalyzed hydrolysis of the equilibrium mixture has been known to afford the lactol (**6**).[6] It suggested that one-pot operation, an acid-catalyzed hydrolysis and hydride reduction, might readily afford the key intermediate, allylic diol (**7**). Thus, oxalic aicd-catalyzed hydrolysis of the equilibrium mixture and subsequent sodium borohydride reduction in water-acetonitrile yielded the anticipated allylic diol (**7**) in 81 % (Scheme 1).



Scheme 1. **a**. anhydrous Na_2CO_3, 32 % peracetic acid, CH_2Cl_2, rt, 2 h, 71 % **b**. 5.0 mol % oxalic acid, H_2O, rt, 12 h **c**. $NaBH_4$, CH_3CN, rt, 4 h, 81 % (from step **b**)

At this stage, the diol (**7**) could be carbonated for the Pd(0)-catalyzed coupling reaction with a nucleoside base. Treatment of the diol (**7**) with methyl chloroformate and DMAP afforded the dicarbonate (**8**) in 92 % yield.[7] The key coupling was then effected by treatment of the dicarbonate (**8**) with 2-amino-6-chloropurine in 1:1 THF:DMSO in the presence of 5 mol % $Pd[P(OPr^i)_3]_4$, which furnished the desired coupling adduct (**9**) and its isomer (**10**) as a 10:1 mixture in 80 % isolated yield (Scheme 2).[8] The attack of purine base on the π-allylpalladium complex proceeds *via* 1,4-addition rather than 1,2-addition presumably because of steric hindrance to 1,2-addition due to the non-bonded interaction from the substituent in the cyclopentene ring. Hydrolysis of this mixture with aqueous sodium hydroxide gave (±)-homocarbovir (**2**) in 73 % yield. In summary, the synthesis of a carbovir analogue, (±)-homocarbovir (**2**), was achieved from 2,5-norbornadiene (**3**) in six steps and 31 % overall yield.



Scheme 2. **a**. pyridine, DMAP, methyl chloroformate, CH_2Cl_2, 0 °C, 2 h, 92 % **b**. i) $Pd(OAc)_2$, (i-PrO)$_3$P, THF, rt ii) n-BuLi, rt iii) **8** in THF, 2-amino-6-chloropurine, DMSO, rt, 23 h (**9**:**10** = 10:1, 80 %) **c**. 1.0 *N* NaOH, reflux, 2 h (73 %)

(±)-Homocarbovir (**2**) was evaluated for cytotoxicity against Vero (African green monkey kidney cell) and MT-4 (HTLV-1-infected human T lymphocyte) and for antiviral activity with herpes simplex virus (HSV) and human immunodefficiency virus (HIV). Unfortunately, antiviral screening revealed that (±)-homocarbovir (**2**) did not exhibit any anti-HSV and anti-HIV activity.

EXPERIMENTAL

Uncorrected melting points were determined with a capillary Büchi 530 melting point apparatus. 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 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.[9] Reagents and solvents were of reagent grade, and solvents were purified by the known procedure[10] before use.

The mixture of bicyclo[3.1.0]hex-2-en-6-*endo*-carboxaldehyde (4) and 2-oxabicyclo[3.2.1]octa-3,6-diene (5). It

was prepared by the known procedure.[5]

***cis*-5-(2'-Hydroxyethyl)-2-cyclopenten-1-ol (7).** To a mixture of the bicyclic aldehyde (**4**) and the bicyclic enol ether (**5**) (0.501 g, 4.63 mmol) in water (20.0 mL) was added oxalic acid (0.0292 g, 0.232 mmol) at rt. After being stirred for 12 h at rt, acetonitrile (25 mL) was added to the reaction mixture. Then, sodium borohydride (0.263 g, 6.95 mmol) was added portionwise over 10 min. After being stirred for 4 h, the reaction mixture was concentrated by rotary-evaporation. The crude reaction mixture was diluted with CH_2Cl_2 (40.0 mL). The organic phase was separated, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (ether, R_f = 0.21) to give a colorless oil (**7**) (0.480 g, 81 %): Spectral data were confirmed by the reported data.[4]

***cis*-3-Methoxycarbonyloxy-4-[2'-(methoxycarbonyloxy)ethyl]cyclopentene (8).** To a solution of diol (**7**) (0.0928 g, 0.724 mmol) in CH_2Cl_2 (3.0 mL) was added pyridine (0.590 mL, 7.24 mmol) and DMAP (0.00440 g, 0.0360 mmol) at 0 °C under argon. Then, methyl chloroformate (0.560 mL, 7.24 mmol) was slowly added. After being stirred for 2 h, the reaction mixture was diluted with CH_2Cl_2 (5.0 mL) and washed with brine (5.0 mL). The aqueous phase was extracted with CH_2Cl_2 (5.0 mL x 3). The organic phase was collected, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (ether/hexane = 1/4, v/v, R_f = 0.20) to give a colorless oil (**8**) (0.163 g, 92 %): Spectral data were compared with those reported by Vince[4a] and Olivo.[4c]

***cis*-2-Amino-6-chloro-9-[4'-methoxycarbonyloxyethyl-2'-cyclopenten-1'-yl]purine (9).** Triisopropyl phosphite (95 %, 0.040 mL, 0.159 mmol) was added at 25 °C to a solution of $Pd(OAc)_2$ (98 %, 0.0045 g, 0.022 mmol) in dry THF (1.0 mL) under argon. After being stirred for 15 min, *n*-BuLi (2.0 *N* in hexane, 0.020 mL, 0.040 mmol) was added at 25 °C. The resulting mixture was stirred for 15 min to obtain tetrakis(triisopropylphosphite)palladium(0) catalyst. The *in situ* prepared Pd(0) catalyst was added to a solution of 2-amino-6-chloropurine (0.0731 g, 0.426 mmol) in DMSO (3.0 mL) *via* cannula at 25 °C. Then, a solution of dicarbonate (**8**) (0.0868 g, 0.355 mmol) in dry THF (2.0 mL) was added to the reaction mixture. After being stirred for 23 h, the reaction mixture was diluted with ethyl acetate (4.0 mL) and washed with saturated brine solution (10 mL). The aqueous phase was extracted with ethyl acetate (5.0 mL x 5). The organic phase was collected, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (1st ether/hexane = 3/1, 2nd ether only, v/v) to give a yellow gummy solid mixture, **9** and **10** (R_f = 0.20 in the 2nd eluent system; **9**/**10** = 10/1, 0.0910 g, 80 %) with stating material **8** (R_f = 0.71 in the 1st eluent system; 0.0046 g, 6.3 %). Spectral data were compared with

those reported by Olivo.[4c]

***cis*-2-Amino-6-hydroxy-9-[4'-hydroxyethyl-2'-cyclopenten-1'-yl]purine (2).** Coupling product mixture **9/10** (0.106 g, 0.314 mmol) was added to 1.0 *N* aqueous NaOH (9.50 mL, 9.50 mmol). The resulting mixture was heated at reflux for 2 h. Then, the reaction mixture was neutralized to *p*H 7-8 with 4.0 *N* HCl. After removal of water by evaporation, the residue was diluted with methanol (40 mL). To this solution, silica gel (~1.5 g) was added, and then the resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography with $CHCl_3$/MeOH (5/1, v/v, R_f = 0.29), a white solid (**2**) was obtained (0.0597 g, 73 %): mp 216 °C (decomp), lit.,[4a] mp 220 ºC (decomp). Spectral data were compared with those reported by Vince[4a] and Olivo.[4c]

ACKNOWLEDGMENT

The author wishes to acknowledge the financial support of Hanyang University, Korea, made in the program year of 1999.

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7. The combination of methyl chloroformate with DMAP and pyridine gave much better result for the preparation of the dicarbonate (**8**) compared to the previous results.[4a, 4c]
8. The integration of the two H-8 proton chemical shifts of the 2-amino-6-chloropurine (δ 7.79 and 7.59) was compared for the determination of the ratio of isomers; Compound (**10**) could be confirmed by the checking allylic protons at C-4' in ^{1}H NMR spectrum (Two allylic protons at C-4' show up at 2.68 ppm).
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