Stereoselective Synthesis of a Novel Carbocyclic Nucleoside

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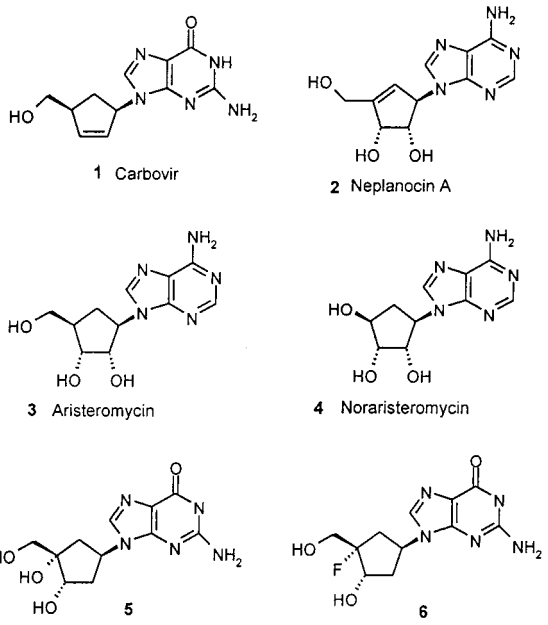
The perpetual interest in carbocyclic nucleosides arose because many normal nucleosides are chemically and enzymatically less stable, but more importantly toxic and resistant prone.[1] Carbocyclic dideoxy nucleosides drugs such as carbovir (**1**), neplanocin A (**2**), aristeromycin (**3**), and nor-aristeromycin (**4**) have attracted unprecedented attention because of potent activity and enhanced stability.[2]



Introduction of an efficient strategy by Trost,[3] founded on Pd-catalyzed allylic rearrangement of cyclic allylic substrate leading to the addition of a nucleoside base with concomitant installation of a double bond, has indeed enabled synthesis of several complex unsaturated nucleosides.[4]

Structurally modified cyclopentane nucleosides (**5** and **6**), containing a stereochemically well-defined tertiary hydroxyl/fluoro group, have been shown to posess potent activity against viruses with a low level of toxicity.[2,5] To our knowledge, no attempts have yet been made to synthesize and screen those novel carbocyclic nucleosides having both a tertiary hydroxyl group and unsaturation. This report describes a strategy to synthesize such carbocyclic nucleoside.

Starting from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**), the requisite 3-*C*-allyl derivative (**8**) was prepared in two high-yielding steps.[6] Subsequent protection of the tertiary hydroxy group with MPM-bromide in the presence of NaH−THF gave **9**. The characteristic signals of MPM group were visualized in the ^{1}H NMR spectrum of **9**. Successive transformations such as (1) acid hydrolysis of the 5,6-acetonide group, (2) mesylation of the resulting diol, and (3) olefination with NaI in 2-butanone gave the diene derivative **10** (Scheme 1).

Ring-closing metathesis[7] of **10** using Grubbs' catalyst at room temperature gave the bicyclic derivative **11**. The ^{1}H NMR spectrum of **11** indicated signals corresponding to olefinic protons at 5.9 ppm, whereas the carbocyclic methylene protons appeared at 2.33 and 2.86 ppm as double doublets. Transformation of **11** into the diol derivative (**12**) was accomplished by (1) hydrolysis of the isopropylidene group, (2) $NaIO_4$-promoted oxidative cleavage, and (3) $NaBH_4$ reduction. Compound **12** was converted into the cyclic carbonate (**13**) using carbonyl diimidazole in refluxing benzene. The ^{1}H and ^{13}C NMR and mass spectral studies confirmed the structure of **13**. The Pd-catalyzed allylic rearrangement[2] of **13** with 6-aminopurine in the presence of $(PPh_3)_4Pd$ and DMSO−THF (1:1) gave the unsaturated carbocyclic nucleoside **14**. Removal of MPM group with DDQ in dioxane−H_2O gave the target carbocyclic nucleoside **15**. The ^{1}H and ^{13}C NMR and elemental analysis of **15** provided the structural proof of this molecule.

In conclusion, this paper describes an efficient methodology to prepare carbocyclic nucleosides having two important chromophores, unsaturation, and tertiary hydroxyl center in its structural framework. The antiviral activity of **15** is under investigation and will be published in future.

Experimental Section

The NMR spectra were recorded in $CDCl_3$/CD_3COCD_3/DMSO-d_6 with TMS as an internal standard on AC 200 MHz, DRX 500 MHz. Optical rotations were measured with a digital polarimeter. Mass spectra were recorded on an autospec mass spectrometer. Elemental analyses were done on an elemental analyzer model 1108 EA. Column chromatography was carried out with silica gel (60−120 mesh). TLC was performed on 0.25 mm precoated silica gel plates (60F-254) with UV or I_2 or anisaldehyde reagent in ethanol. Light petroleum refers to a mixture of hexanes with bp 60−80 °C.

3-*C*-Allyl-1,2;5,6-di-*O*-isopropylidene-3-*O*-(4-methoxyphenylmethyl)-α-D-allofuranose (9). Compound **8**[6] (9.0 g, 30.0 mmol) in THF (30 mL) was added to a solution of sodium hydride (50% dispersion in oil, 2.16 g, 45.0 mmol washed with 10 mL of hexane) in THF (50 mL). After 1 h at room temperature, MPM bromide (7.23 g, 36.0 mmol) in THF (20 mL) was added, and the mixture was stirred for 6 h and then concentrated. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified on silica gel by using

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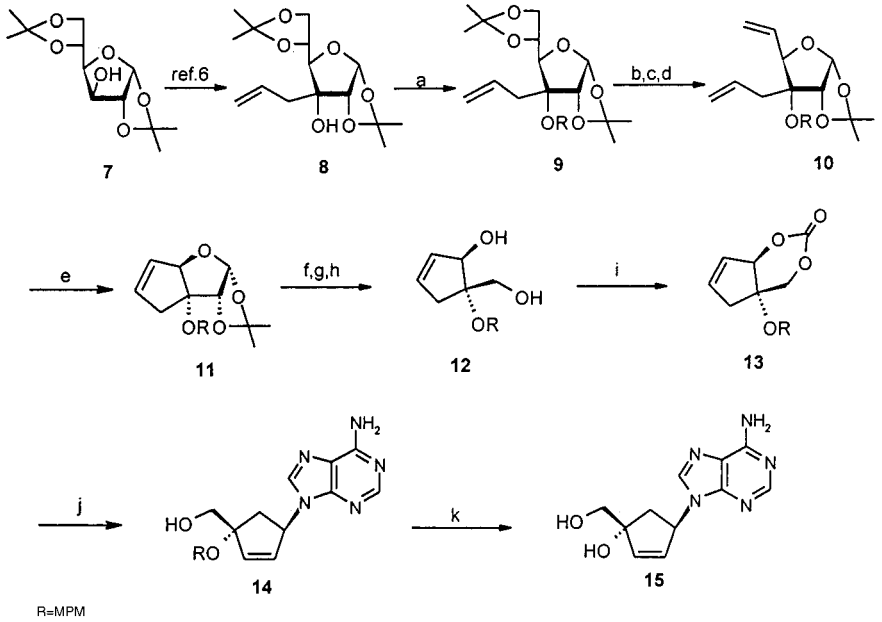
Scheme 1[a]



[a] Key: (a) MPM-Br/NaH, THF, rt, 6 h; (b) 0.8% H_2SO_4, MeOH, rt, 10 h; (c) $MeSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; (d) NaI, EtCOMe, reflux, 8 h; (e) Grubbs' catalyst, CH_2Cl_2, rt, 6 h; (f) 0.4% H_2SO_4, dioxane, reflux, 2 h; (g) $NaIO_4$, CH_2Cl_2, SiO_2, rt, 1 h; (h) $NaBH_4$, MeOH, rt, 1 h; (i) Im-CO-Im, C_6H_6, reflux, 4 h; (j) 6-aminopurine, $Pd(PPh_3)_4$, DMSO/THF (1:1), 45 °C, 2 h; (k) DDQ, $MeCN/H_2O$, rt, 2 h.

hexanes−ethyl acetate (4:1) to give **9** (10.83 g, 86%), as a liquid: $[\alpha]_D$ +62° (*c* 2.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32, 1.38, 1.43, 1.63 (4s, 12 H), 2.42 (dd, 1 H, J = 6.45, 12.9 Hz), 2.67 (dd, 1 H, J = 3.9, 12.9 Hz), 3.77 (s, 3 H), 3.93 (m, 1 H), 4.09 (m, 1 H), 4.16 (m, 2 H), 4.45 (d, 1 H, J = 3.2 Hz), 4.68 (ABq, 2 H, J = 12.9 Hz), 5.32 (m, 2 H), 5.61 (d, 1 H, J = 3.2 Hz), 6.00 (m, 1 H), 6.84 (d, 2 H, J = 8.0 Hz), 7.29 (d, 2 H, J = 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.1, 26.3, 26.7, 35.6, 54.9, 66.4, 67.6, 72.8, 81.0, 82.7, 83.3, 103.2, 109.2, 112.3, 113.2, 118.2, 128.4, 131.07, 132.5; EIMS *m*/*z* 420 (M^+). Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.71; H, 7.62. Found: C, 65.33; H, 7.40.

3-*C*-Allyl-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-(4-methoxyphenylmethyl)-α-D-*ribo*-hex-5-enofuranose (10). Compound **9** (8.4 g, 20.0 mmol) and 0.8% sulfuric acid (3 mL) in methanol (50 mL) were stirred at room temperature for 10 h and neutralized with solid $NaHCO_3$. The solid was filtered, and the filtrate was concentrated. The residue was purified on silica gel with $CHCl_3$−MeOH (10:1) to afford the 5,6-diol (5.7 g, 75%), as a thick liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37, 1.62 (2s, 6 H), 2.62 (m, 2 H), 3.62 (dd, 1 H, J = 6.2, 12.5 Hz), 3.75 (dd, 1 H, J = 4.7, 12.5 Hz), 3.78 (s, 3 H), 3.90 (m, 1 H), 4.06 (d, 1 H, J = 10.0 Hz), 4.47 (d, 1 H, J = 3.1 Hz), 4.62 (s, 2 H), 5.25 (m, 2 H), 5.65 (d, 1 H, J = 3.1 Hz), 6.0 (m, 1 H), 6.90 (d, 2 H, J = 7.5 Hz), 7.34 (d, 2 H, J = 7.5 Hz). It was taken up in Et_3N (6.3 mL), DMAP (0.18 g), and CH_2Cl_2 (30 mL), and $MeSO_2Cl$ (3.6 mL, 36.0 mmol) was added. After 1 h, the reaction mixture was washed with saturated Na_2CO_3 and water, dried (Na_2SO_4), and concentrated. The crude dimesylate (7.4 g, 13.8 mmol) and NaI (10.34 g, 69.0 mmol) in 2-butanone (50 mL) were heated under reflux for 8 h and concentrated. The residue was partitioned between ethyl acetate and saturated sodium thiosulfate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude was purified by silica gel with hexanes−ethyl acetate (9:1) to give **10** (3.33 g, 64%) as a liquid: $[\alpha]_D$ +53° (*c* 2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38, 1.60 (2s, 6 H), 2.31 (dd, 1 H, J = 6.1, 13.5 Hz), 2.55 (dd, 1 H, J = 6.3, 13.5 Hz), 3.78 (s, 3 H), 4.44 (m, 3 H), 4.53 (s, 2 H), 4.60 (d, 1 H, J = 3.0 Hz), 5.0−5.5 (m, 4 H), 5.64 (d, 1 H, J = 3.0 Hz), 5.9 (m, 2 H), 6.8 (m, 2 H), 7.23 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.4, 26.7, 35.8, 55.0, 71.3, 81.5, 81.6, 84.0, 103.6, 112.3, 117.7, 117.9, 128.5−130.3, 132.3, 132.7; EIMS *m*/*z* 346 (M^+). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.36; H, 7.51. Found: C, 69.01; H, 7.42.

(2*R*,3*R*,4*S*,5*R*)-2,3-*O*-Isopropylidene-4-*O*-(4-methylphenylmethyl)-1-oxabicyclo[3.3.0]oct-6-ene (11). Compound **10** (1.73 g, 5.0 mmol) and Grubbs' catalyst (0.20 g) in CH_2Cl_2 (50 mL) were stirred for 6 h at room temperature and then evaporated. The residue was purified on silica gel with hexanes−ethyl acetate (4:1) to give **11** (1.27 g, 80%), as a solid: mp 79−81 °C; [α] +24° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35, 1.60 (2s, 6 H), 2.33 (brd, 1 H, J = 17.5 Hz), 2.86 (dd, 1 H, J = 1.0, 17.5 Hz), 3.77 (s, 3 H), 4.43 (d, 1 H, J = 9.2 Hz), 4.52 (d, 1 H, J = 3.0 Hz), 4.64 (d, 1 H, J = 9.2 Hz), 4.98 (brs, 1 H), 5.81 (d, 1 H, J = 3.0 Hz), 5.90 (m, 2 H), 6.81 (d, 2 H, J = 7.7 Hz), 7.26 (d, 2 H, J = 7.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.2, 37.6, 39.6, 54.9, 67.3, 83.3, 90.5, 91.0, 106.5, 113.4, 128.9, 130.3, 134.0; EIMS *m*/*z* 318 (M^+). Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.92; H, 6.91. Found: C, 68.12; H, 6.85.

(1*S*,2*R*)-1-(4-Methoxyphenylmethoxy)-1-hydroxymethylcyclopent-3-en-2-ol (12). Compound **11** (3.81 g, 12.0 mmol), dioxane (30 mL), and 0.4% H_2SO_4 (40 mL) were heated under reflux for 2 h. The reaction mixture was neutralized with saturated Na_2CO_3 and evaporated. The residue was extracted with ethyl acetate, dried (Na_2SO_4), and concentrated to give crude hemiacetal (3.17 g). The above product (3.17 g, 11.4 mmol) was vigorously stirred with CH_2Cl_2 (30 mL), 0.65 M $NaIO_4$ solution (25 mL), and chromatography grade SiO_2 (20 g) for 1 h. The solid was filtered and washed with CH_2Cl_2. The combined filtrate was evaporated and then dissolved in MeOH (30 mL). Solid $NaBH_4$ (0.5 g) was added, and after 1 h at room temperature, the reaction mixture concentrated. The residue was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), concentrated, and purified by silica gel by eluting with hexanes−ethyl acetate (3:1) to give **12** (2.1 g, 70%), as a thick liquid: $[\alpha]_D$ −78° (*c* 2.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (q, 2 H, J = 16.1 Hz), 3.89 (s, 3 H), 3.95 (m, 3 H), 4.43 (ABq, 2 H, J = 12.9 Hz), 4.91 (s, 1 H), 5.77 (brs, 1 H), 6.84 (d, 2 H, J = 8.5 Hz), 7.25 (d, 2 H, J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.8, 55.2, 64.0, 65.2, 82.9, 87.6, 128.7, 131.9, 132.5; EIMS *m*/*z* 250 (M^+).

(1*S*,2*R*)-5-(4-Methoxyphenylmethoxy)-1,3-dioxabicyclo[4.3.0]non-7-en-2-one (13). A solution of compound **12** (0.275 g, 1.1 mmol) and *N*,*N*′-carbonyldiimidazole (0.27 g, 1.65 mmol) in benzene (5 mL) was heated under reflux for 4 h and concentrated. The residue was purified on silica gel with hexanes−ethyl acetate (9:1) as eluent to give **13** (0.21 g, 69%) as a colorless liquid: $[\alpha]_D$ 40° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.53 (d, 1 H, J = 12.7 Hz), 2.82 (d, 1 H, J = 12.7 Hz), 3.78 (s, 3 H), 4.07 (d, 1 H, J = 7.0 Hz), 4.48 (m, 4 H), 5.41 (s, 1 H), 5.82 (m, 1 H), 6.04 (m, 1 H), 6.81 (d, 2 H, J = 6.8 Hz), 7.25 (d, 2 H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.0, 55.1,

66.0, 68.7, 81.2, 91.7, 128.2, 128.8, 129.2, 134.9, 150.4; EIMS *m*/*z* 276 (M^+). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.79. Found: C, 64.88; H, 5.62.

(1′*R*,4′*R*)-(4′-Hydroxy-4′-hydroxymethylcyclopen-2′-enyl)adenine (15). To a solution of 6-aminopurine (73 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (62 mg) in DMSO (2 mL) under nitrogen was added **13** (150 mg, 0.54 mmol) in THF (2 mL). After being stirred for 2 h at 45 °C, the reaction mixture was diluted with water and repeatedly extracted with ethyl acetate. The combined organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel with ethyl acetate−MeOH (9:1) to give compound **14** (108 mg, 54%) as a colorless solid: mp 167−169 °C; $[\alpha]_D$ +124° (*c* 1, MeOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.10 (dd, 1 H J = 4.7, 13.3 Hz), 2.66 (dd, 1 H, J = 6.0, 13.3 Hz), 3.53 (d, 1 H, J = 12.6 Hz), 3.76 (s, 3 H), 4.36 (t, 2 H, J = 13.3 Hz), 5.83 (brs, 1 H), 6.23 (m, 2 H), 6.90 (d, 2 H, J = 6.8 Hz), 7.26 (d, 2 H, J = 6.8 Hz), 8.10 (s, 1 H), 8.20 (s, 1 H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 39.0, 55.8, 59.7, 65.2, 66.2, 92.0, 129.9, 131.8, 135.0, 139.0, 152.4.

The above product **14** (91 mg, 0.25 mmol) and DDQ (85 mg) in dioxane containing two drops of water (3 mL) were stirred at room temperature for 2 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel with ethyl acetate−MeOH (5:1) to give compound **15** (44 mg, 72%) as a thick syrup: $[\alpha]_D$ + 82° (*c* 0.3, MeOH); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 2.33 (dd, 1 H, J = 3.3, 14.8 Hz), 2.60 (dd, 1 H, J = 6.6, 14.8 Hz), 3.70 (ABq, 2 H, J = 13.3 Hz), 5.90 (m, 1 H), 6.16 (m, 1 H), 6.26 (brs, 1 H), 8.03 (s, 1 H), 8.20 (s, 1H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 42.7, 59.2, 67.8, 85.2, 132.0, 139.2, 140.9, 152.7. Anal. Calcd for $C_{11}H_{13}N_5O_2$: C, 53.44; H, 5.26. Found: C, 53.39; H, 5.60.

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Supporting Information Available: ^{1}H NMR spectra of **11, 12, 13, 14** and **15** and ^{13}C NMR of **11**, **14** and **15.** This material is available free of charge via Internet at http://pubs.acs.org.

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