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Enantioselective syntheses of 5′-*homo*-carbocyclic nucleosides

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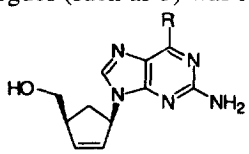
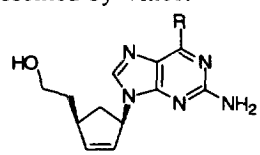
Abstract: Efficient enantioselective syntheses of 5′-*homo*-carbocyclic nucleosides (**3** and **4**) starting from (−)-4-*endo*-hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one (**5**) are presented.

Interest in analogues of the selective HIV-1 replication inhibitor 2′,3′-didehydro-2′,3′-dideoxyguanosine, carbovir (**1**) and its cyclopropylamine congener, 1592U89 (**2**) is emerging from the search for more lipophilic and potent anti-HIV agents.[1] A racemic synthesis of 4′-hydroxyethyl carbonucleoside analogues (such as **3**) was recently presented by Vince.[2]



1 R= OH **carbovir**
2 R= $NHCH(CH_2)_2$ **1592U89**

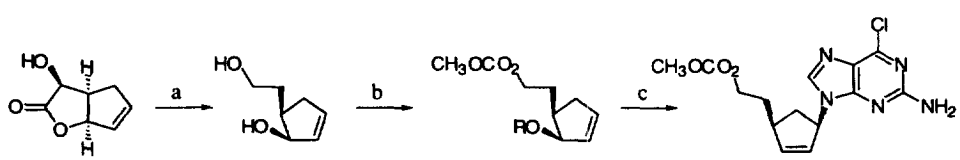


3 R= OH
4 R= $NHCH(CH_2)_2$

We present in this paper, a short enantioselective synthesis of 5′-*homo*-carbocyclic nucleosides, represented by 5′-*homo*-carbovir (**3**) and 5′-*homo*-1592U89 (**4**), starting from (−)-4-*endo*-hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one (**5**). Chirality is introduced enzymatically by kinetic resolution of the α-hydroxylactone **5**, and a two step reduction of the α-hydroxylactone is applied to obtain chiral key intermediate **6** (Figure 1).

endo-Hydroxylactone **5** has proved to be a valuable building block for the preparation of carbonucleosides,[3] sesbanimides,[4] brefeldin A,[5] and hypocholesterolemic agents.[6] Hydroxylactone **5** was obtained by the water-promoted reaction of glyoxylic acid with cyclopentadiene,[7] and was enzymatically resolved using either *Pseudomonas fluoresecens* lipase or Amano lipase PS.[8]

A two step protocol was applied to reduce optically pure hydroxylactone **5** to the desired allylic diol **6**. Reduction of hydroxylactone **5** was accomplished by Aggarwal's bromination procedure using triphenylphosphine and zinc bromide,[9] followed by treatment of the resulting bromide with lithium aluminium hydride in 90% yield, Figure 1. Treatment of diol **6** with methyl chloroformate provided



5 **6** **7** R= CO_2CH_3 **8** R= H **9**

Figure 1. Reagents: a, i) see Aggarwal *et al.*,[9] ii) $LiAlH_4$, THF; b, $ClCO_2Me$, pyridine, CH_2Cl_2; c, 2-amino-6-chloropurine, $Pd(PPh_3)_4$, THF–DMSO.

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a mixture of dicarbonate **7** (70%) and monocarbonate **8** (11%). Recovered monocarbonate **8** was recycled.

An attractive convergent approach to carbocyclic nucleosides consists of Trost's palladium-catalyzed coupling of purine bases with allylic carbonates or acetates.[10] Thus, coupling of allylic dicarbonate **8** with 2-amino-6-chloropurine provided the purine carbonate adduct **9** (60%). Hydrolysis of carbonate **9** with aqueous sodium hydroxide gave 5′-*homo*-carbovir **3** (72%). Treatment of purine adduct **9** with cyclopropylamine followed by basic hydrolysis provided 5′-*homo*-1592U89 **4** (two steps, 69%).

In summary, optically pure 5′-*homo*-carbocyclic nucleosides **3** and **4** were easily prepared in a convergent synthesis starting from enzymatically resolved hydroxylactone **5**. This practical methodology can also provide the opposite enantiomer or racemic 5′-*homo*-carbocyclic nucleosides.

Experimental section

General

Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. ^{1}H-NMR (360 MHz) and ^{13}C-NMR (90 MHz) spectra were obtained with a Bruker WM-360 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm tube. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer.

(1R,5R)-5-(2′-Hydroxyethyl)-2-cyclopenten-1-ol **6**[11]

(−)-*endo*-Hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one **5** was brominated according to reported procedure.[9] A solution of bromolactone (3.79 g, 18.64 mmol) in dry THF (50 ml) was added dropwise to a solution of lithium aluminium hydride (1.426 g, 37.57 mmol) in dry THF (150 ml). The mixture was stirred at reflux for 12 h. Diethyl ether saturated with water (25 ml) was added dropwise with vigorous stirring, followed by water (4 ml), at such a rate that gentle reflux was maintained to give a gray precipitate. The mixture was stirred at reflux for 1 h and then allowed to stand for 15 min. The supernatant liquid was decanted and filtered through Celite filter agent. Tetrahydrofuran (50 ml) and water (2 ml) were added to the precipitate which was stirred at reflux for 1 h and then the hot mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatography. Elution with 5% methanol in chloroform gave compound **6** as a colorless oil: 2.15 g (90% yield). $[\alpha]_{25}$ −80.7 (*c* 0.81, $CHCl_3$); IR 3520–3200, 3057, 2929, 1440, 1062, 1042; ^{1}H-NMR ($CDCl_3$) δ 5.96 (1H, m), 5.83 (1H, m), 4.61 (1H, m), 4.10 (2H, s), 3.71 (1H, m), 3.60 (1H, m), 2.36 (1H, m), 2.12 (2H, m), 1.84 (1H, m), 1.66 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 135.2 (CH), 132.6 (CH), 76.2 (CH), 61.9 (CH_2), 41.1 (CH), 37.4 (CH_2), 31.7 (CH_2).

(1R,5R)-5-(2′-Hydroxyethyl)-2-cyclopenten-1-ol-1,2′-bis-(methylcarbonate) **7**

To a cold solution of diol **6** (1.034 g, 8.07 mmol) and pyridine (1.92 g, 24.3 mmol) in dichloromethane (25 ml) was added methyl chloroformate (7.69 g, 81.4 mmol), followed by a few crystals of DMAP. The solution was stirred at room temperature for 1 h. The solution was washed with 5% HCl (15 ml), sat. $NaHCO_3$ solution (15 ml), and brine (15 ml). The organic solution was dried over $MgSO_4$, filtered and the solvent evaporated in vacuo. The residue was purified by column chromatography. Elution with 10% hexanes in ethyl acetate gave dicarbonate **7** [1.38 g (70% yield)] and monocarbonate **8** [168 mg (11% yield)]. Compound **7**: $[\alpha]_{25}$ −163.3 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 6.13 (1H, m), 5.90 (1H, m), 5.43 (1H, m), 4.16 (2H, m), 3.73 (3H, s), 3.71 (3H, s), 2.50–2.30 (2H, m), 2.17 (1H, m), 1.96 (1H, m), 1.76 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 155.9 (CO), 155.6 (CO), 138.9 (CH), 129.1 (CH), 83.1 (CH), 67.1 (CH), 54.7 (CH_2), 54.6 (CH_2), 38.3 (CH_3), 37.1 (CH_3), 28.0 (CH_2). *(−)-(2-Hydroxy-3-cyclopenten-1-yl)-ethylmethylcarbonate* (**8**): IR 3600–3250, 1748, 1495, 1270; ^{1}H-NMR ($CDCl_3$) δ 6.03 (1H, m), 5.92 (1H, m), 4.61 (1H, dt, *J* 6, 2.2 Hz), 4.27 (2H, m), 3.78 (3H, s), 2.43 (1H, m), 2.27–1.98 (3H, m), 1.81 (1H, m), 1.52 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ 155.8 (CO), 135.3 (CH), 133.0 (CH), 76.0 (CH), 67.7 (CH), 54.6 (CH_2), 39.1 (CH_3), 36.6 (CH_2), 28.1 (CH_2).

(1R,4R)-Methyl [4-(2′-amino-6′-chloro-purin-9′-yl)-2-cyclopenten-1-yl]-ethylcarbonate **9**

To a solution of 2-amino-6-chloropurine (85 mg, 0.5 mmol) in dimethylsulfoxide (1.5 ml) was added $Pd(PPh_3)_4$ (60 mg, 0.05 mmol), followed by a solution of dicarbonate **7** (122 mg, 0.5 mmol) in THF (1.5 ml). The solution was stirred at room temperature for 1 h. The solution was poured over water (10 ml) and extracted with ethyl acetate (3×7 ml). The combined organic layers were washed with brine (10 ml), dried over $MgSO_4$, filtered and the solvent evaporated in vacuo. The residue was purified by column chromatography. Elution with 40% hexanes in ethyl acetate gave compound **9**: 101.5 mg (60% yield). $[\alpha]_{25}$ −54.4 (*c* 0.89, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.79 (1H, s), 6.19 (1H, dt, *J* 5.6, 2 Hz), 5.86 (1H, dt, *J* 5.6, 2 Hz), 5.53 (1H, m), 5.20 (2H, bs), 4.25 (2H, m), 3.78 (3H, s), 3.0–2.83 (2H, m), 1.98 (1H, m), 1.81 (1H, m), 1.62 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 159.2 (CH), 155.7 (CO), 153.5 (C), 151.0 (C), 140.5 (CH), 140.4 (CH), 128.5 (CH), 125.4 (C), 66.3 (CH_3), 59.8 (CH_2), 54.8 (CH), 41.7 (CH), 38.2 (CH_2), 34.3 (CH_2).

(1′R,4′R)-2-Amino-6-hydroxy-9-[4′-(hydroxyethyl)-2′-cyclopenten-1′-yl]-purine **3**

A solution of compound **9** (96.8 mg, 0.286 mmol) in aqueous 0.33 N NaOH solution (1.5 ml) was stirred at reflux for 1 h. Solvent was removed in vacuo, and the residue was purified by column chromatography. Elution with 15% methanol in dichloromethane gave compound **3**: 54.1 mg (72% yield). $[\alpha]_{25}$ −48.3 (*c* 0.3, DMSO); ^{1}H-NMR was identical to that reported by Vince;[2a] ^{13}C-NMR (DMSO-d_6) δ 157.0 (C), 153.5 (C), 150.9 (C), 140.5 (CH), 134.9 (CH), 128.4 (CH), 116.8 (C), 59.3 (CH_2), 58.7 (CH), 41.4 (CH), 38.6 (CH_2), 38.3 (CH_2).

(1R,4R)-Methyl [4-(2′-amino-6′-cyclopropylamino-purin-9′-yl)-2-cyclopenten-1-yl]-ethylcarbonate

A solution of compound **9** (92 mg, 0.272 mmol) in ethanol (3 ml) was treated with cyclopropylamine (155 mg, 2.72 mmol). The solution was stirred at reflux for 12 h. Solvent was removed in vacuo, and the residue was purified by column chromatography. Elution with 5% methanol in dichloromethane gave the title compound: 93.6 mg (96% yield). ^{1}H-NMR ($CDCl_3$) δ 7.49 (1H, s), 6.13 (1H, m), 5.83 (2H, m), 5.50 (1H, m), 4.89 (2H, bs), 4.23 (2H, m), 3.78 (3H, s), 3.01 (1H, m), 2.88 (2H, m), 1.95 (1H, m), 1.77 (1H, m), 1.53 (1H, m), 0.86 (2H, m), 0.61 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 159.9 (C), 156.2 (CO), 155.6 (C), 151.0 (C), 139.4 (CH), 135.1 (CH), 129.2 (CH), 113.0 (C), 66.2 (CH_3), 58.7 (CH_2), 54.6 (CH), 41.5 (CH), 38.7 (CH_2), 34.5 (CH_2), 23.5 (CH), 7.2 ($2CH_2$).

(1′R,4′R)-2-Amino-6-cyclopropylamino-9-[4′-(hydroxyethyl)-2′-cyclopenten-1′-yl]-purine **4**

A solution of carbonate (60 mg, 0.167 mmol) in aqueous 0.33 N NaOH solution (6 ml) was stirred at reflux for 1 h. Solvent was removed in vacuo, and the residue was purified by column chromatography. Elution with 10% methanol in dichloromethane gave compound **4**: 36.3 mg (72% yield). $[\alpha]_{25}$ −51.6 (*c* 0.7, MeOH); ^{1}H-NMR (DMSO-d_6) δ 7.57 (1H, s), 7.25 (1H, s), 6.14 (1H, m), 5.83 (3H, m), 5.36 (1H, m), 4.46 (1H, m), 3.48 (2H, m), 3.04 (1H, bs), 2.82 (1H, m), 2.67 (1H, dt, *J* 13.4, 8.2), 1.69 (1H, m), 1.49 (2H, m), 0.66 (2H, m), 0.58 (2H, m); ^{13}C-NMR (DMSO-d_6) δ 160.1 (C), 155.9 (C), 151.1 (C), 140.1 (CH), 134.6 (CH), 128.7 (CH), 113.7 (C), 59.3 (CH_2), 58.2 (CH), 41.4 (CH), 38.6 (CH_2), 38.2 (CH_2), 23.8 (CH), 6.4 ($2CH_2$).

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