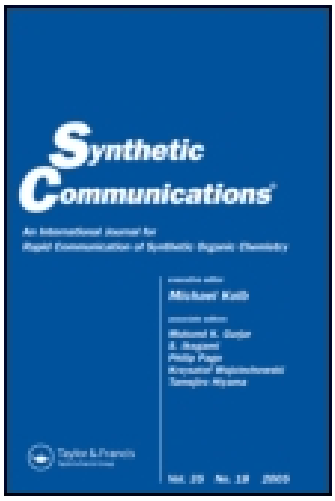

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A Facile Synthesis of (-)-(4R,5R)-4,5-(Isopropylidenedioxy)-2-cyclopentenone, a Useful Precursor to d-Like Carbanucleosides

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A Facile Synthesis of (−)-(4*R*,5*R*)-4,5-(*Iso*propylidenedioxy)-2-cyclopentenone, a Useful Precursor to D-Like Carbanucleosides

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ABSTRACT

A facile synthesis of (−)-(4*R*,5*R*)-4,5-(*iso*propylidenedioxy)-2-cyclopentenone ((−)-**2**), as a precursor to D-like carbanucleosides, is described in 5 steps from (1*S*,4*R*)-4-acetoxycyclopent-2-en-1-ol (**3**). Compound **3** has also been described in the literature as amenable to the formation of (+)-**2**, thus making both the D-like and L-like carbanucleosides available from the same readily available **3**.

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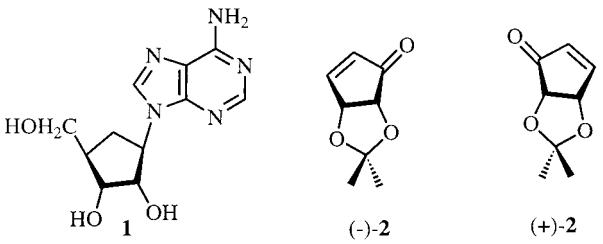
INTRODUCTION

While carbanucelosides have been studied since the synthesis of carbocyclic adenosine (**1**, aristeromycin) by Southern Research Institute,[1] a renaissance has occurred with this series of compounds as a result of their promising biological properties.[2] Our laboratory is contributing to this revival[3] and recently sought a route to C-5′ varied D-like and L-like carbanucleosides that would begin with the Michael addition reaction of a functionalized carbon nucleophile to the C-3 center of an appropriately protected 4,5-dihydroxy-2-cyclopentenone (that is, (−)-**2** for D-like analogs and (+)-**2** for the L-like enantiomers) (Sch. 1). The literature[4] provided a means to (+)-**2** but our experience has shown that the existing procedures[5] to (−) **2** have limitations of various types. Using the same starting material as described[4] for (+)-**2** (that is, (1*S*,4*R*)-4-acetoxycyclopent-2-en-1-ol (**3**)) we report here an efficient and convenient route to (−)-**2**. This, in turn, will permit preparation of the desired carbanucleosides in both the D-like and L-like forms from a common precursor (**3**).

RESULTS

The synthesis of (−)-**2** began with the conversion of **3** to the monophosphate **4** via a procedure developed in our laboratories.[6] Glycolization of **4** to **5** was followed by catalization to **6**. Ammonolysis of **6** provided **7**, which was then subjected to oxidative elimination using pyridinium chlorochromate[4,7] to give (−)-**2** whose properties compared favorably with those recently repored.[5]



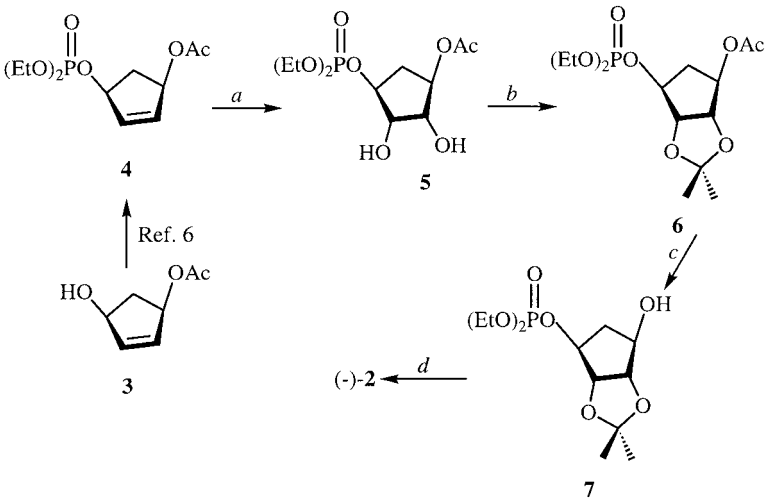
Scheme 1.

EXPERIMENTAL

General Methods

Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA. ^{1}H spectra were recorded on a Bruker AC 250 spectrometer, referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), and m (multiplet). Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica gel, 230–400 mesh, 60 Å and elution with the indicated solvent systems. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials. Carbon–phosphorus coupling was observed in the ^{13}C NMR spectra for **5** and **7**.

(1*S*,2*S*,3*S*,4*R*)-4-Acetoxy-2,3-dihydroxycyclopentan-1-yl diethyl phosphate (5): To an ice-water cooled solution of (1*S*,4*R*)-4-acetoxycyclopent-2-en-1-yl diethyl phosphate **4**[6] (Sch. 2) (2.78 g, 10 mol) in acetone (20 mL) and H_2O (4 mL) was added *N*-methylmorpholine *N*-oxide (4.1 mL, 50% aq)



Scheme 2. Reaction conditions: *a*, *N*-methylmorpholine *N*-oxide/catalytic OsO_4 in acetone/H_2O; *b*, 2,2-dimethoxypropane/acetone/catalytic *p*-TsOH; *c*, NH_3 in MeOH; *d*, pyridinium chlorochromate and Celite in CH_2Cl_2.

and OsO_4 (20 mg). The mixture was then stirred at r.t. for 24 h. The solution was evaporated under vacuum and the residue subjected to column chromatographic purification with hexanes–EtOAc (1:3) to give **5** (2.05 g, 70%); ^{1}H NMR ($CDCl_3$) δ 4.90 (m, 1H), 4.66 (m, 1H), 4.57 (s, 1H), 4.14 (m, 6H), 4.02 (s, 1H), 2.73 (m, 1H), 2.06 (m, 3H), 1.71 (m, 1H), 1.31 (m, 6H); ^{13}C NMR[8] ($CDCl_3$) δ 170.74, 80.96, 80.87, 77.48, 76.47, 76.27, 76.20, 64.12, 35.04, 34.95, 20.82, 15.88,15.79. Anal. calcd. for $C_{11}H_{21}O_8P$: C, 42.31, H, 6.78. Found: C, 42.10, H, 6.82.

(1*S*,2*S*,3*S*,4*R*)-4-Hydroxy-2,3-(*iso*propylidenedioxy)cyclopentan-1-yl diethyl phosphate (7): Compound **5** (10.0 g, 32.05 mmol) was dissolved in solution of anhydrous acetone (100 mL) and 2,2-dimethoxypropane (23 mL). To this was added *p*-toluenesufonic acid (200 mg) and the reaction mixture stirred at r.t. for 15 h. The mixture was then brought to pH 7 with NH_4OH. Following this, the acetone was evaporated under vacuum. The residue was dissolved in EtOAc (200 mL) and this solution washed with brine (3×20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give (1*S*,2*S*,3*S*,4*R*)-4-acetoxy-2,3-(*iso*propylidenedioxy)cyclopentan-1-yl diethyl phosphate (**6**) as a clear oil (11.75 g, 100%); ^{1}H NMR ($CDCl_3$) δ 5.08 (d, $J = 5.25$, 1H), 4.73 (m, 1H), 4.63 (m, 1H), 4.06 (m, 5H), 2.06–2.40 (m, 2H), 2.04 (m, 3H), 1.28–1.48 (m, 12H). Compound **6** obtained in this manner was used directly in the next reaction without further characterization.

A solution of **6** (2.7 g, 7.6 mmol) in dry MeOH (50 mL) saturated with NH_3 was kept at r.t. for 24 h in a Parr stainless steel sealed reaction vessel. The volatiles were removed under reduced pressure and the residue purified via column chromatography using CH_2Cl_2–MeOH (40:1) to yield **7** (2.1 g, 90%); ^{1}H NMR ($CDCl_3$) δ 4.78 (m, 2H), 4.62 (m, 1H), 4.06 (m, 5H), 2.30 (s, 1H), 2.11 (m, 1H), 2.04 (m, 1H), 1.28 1.48 (m, 12H); ^{13}C NMR[8] ($CDCl_3$) δ 110.70, 86.33, 86.02, 85.08, 84.96, 83.23, 83.11, 77.17, 76.73, 64.18, 64.08, 62.52, 62.43, 37.38, 37.32, 26.28, 23.94, 16.15, 16.05. Anal. calcd. for $C_{12}H_{23}O_7P$: C, 46.44, H, 7.47. Found: C, 46.54, H, 7.40.

(−)-(4*R*,5*R*)-4,5-(*Iso*propylidenedioxy)-2-cyclopentenone ((−)-2): To a solution of **7** (1.57 g, 5.1 mmol) in CH_2Cl_2 (20 mL) were added pyridinium chlorochromate (2.47 g) and Celite (4 g). This mixture was stirred for 24 h under N_2 and filtered and the solvent removed in vacuo. Column chromatographic purification of the residue using hexanes–EtOAc (1:3) gave (−)-**2** (0.61 g, 81%) whose ^{1}H and ^{13}C NMR spectra were in agreement with literature values.[5] Anal. calcd. for $C_8H_{10}O_3$: C, 62.33, H, 6.54. Found: C, 62.10, H, 6.59.

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