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Stereocontrolled synthesis of novel 6′(α)-hydroxy carbovir analogues

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Abstract—This paper describes the racemic and stereoselective synthetic route for a novel 6′(α)-hydroxy-carbovir from a simple acyclic precursor, Solketal. The relative stereochemistry of the target nucleosides was successfully controlled by a sequential stereoselective glycolate Claisen rearrangement followed by a ring-closing metathesis (RCM). Adenine and cytosine were coupled using a Pd(0) catalyzed allylic alkylation strategy in a high regio- and stereoselective manner.

1. Introduction

Many natural and synthetic carbocyclic nucleosides have been reported. Carbocyclic nucleosides possess greater metabolic stability against nucleoside phosphorylas,[1] and show interesting antiviral activity against the herpes virus,[2] the human cytomegalovirus,[3] the hepatitis B virus,[4] and the human immunodeficiency virus owing to their structural characteristics.[5] Another interesting feature of carbocyclic nucleosides is that a number of carbocyclic adenosine analogues appear to exert their antiviral action by inhibiting *S*-adenosylhomocysteine hydrolase.[6] Therefore, this mechanism might be exploited in a combination therapy with a nucleoside acting by a different mechanism.[7]

Since the 6′-hydroxymethyl substituted carbovir[8] was reported to exhibit good biological activity as a potent anti-HIV agent, many medicinal chemists have begun to examine the 6′-modified carbocyclic nucleosides including the 6′(β)-hydroxy carbovir analogue, which was reported by Katagiri et al.[9] Moreover, the recent FDA approval of abacavir as an anti-HIV agent has prompted further studies on the use of carbocyclic nucleosides as chemotherapeutic agents.[10]

In this study novel 6′(α)-hydroxy carbovir analogues were synthesized based on the interesting findings from the 6′-modified carbovir analogues as part of our ongoing drug discovery program. This paper reports their synthetic procedures with use of a chelation controlled glycolate Claisen rearrangement and a ring-closing metathesis (RCM) as the key reactions.

2. Results and discussion

It was envisaged that cyclopentenol **11**(**β**) might be constructed using a RCM of **10**. In addition, it was suggested that an acyclic precursor **10** might be prepared from a simple Solketal using a stereoselective α-chelation controlled Claisen rearrangement of compound **7** and an α-chelation controlled nucleophilic addition on carbonyl **9** (Scheme 1).

Cheap and commercially available Solketal was oxidized and converted to the α,β-unsaturated methyl ester **2** using a well-known procedure in a 53% two step yield.[11] The α,β-unsaturated methyl ester **2** was reduced by DIBALH at −78°C in CH_2Cl_2 to give the allylic alcohol **3** in a 92% yield. This was protected by benzyl bromide (BnBr) to give compound **4** (90%). The isopropylidene protecting group of compound **4** was removed by acid hydrolysis to give the diol **5** (95%). The selective mono-silylation of the diol **5** with *t*-butyldimethylsilyl chloride (TBDMSCl) (1.1 equiv.) and imidazole in CH_2Cl_2 at 0°C for 5 h furnished compound **6**, which was then converted to the benzyloxymethyl-protected allylic glycolate ester **7** under DCC and DMAP conditions in a 76% two-step yield.[12]

A sigmatropic rearrangement process was used to convert the allylic glycolate **7** to a γ,δ-unsaturated methyl ester **8** with the correct stereochemistry at *C*-2 and *C*-3. The concept of an acyclic steroeselection has attracted substantial interest with impressive results.[13] Therefore, a

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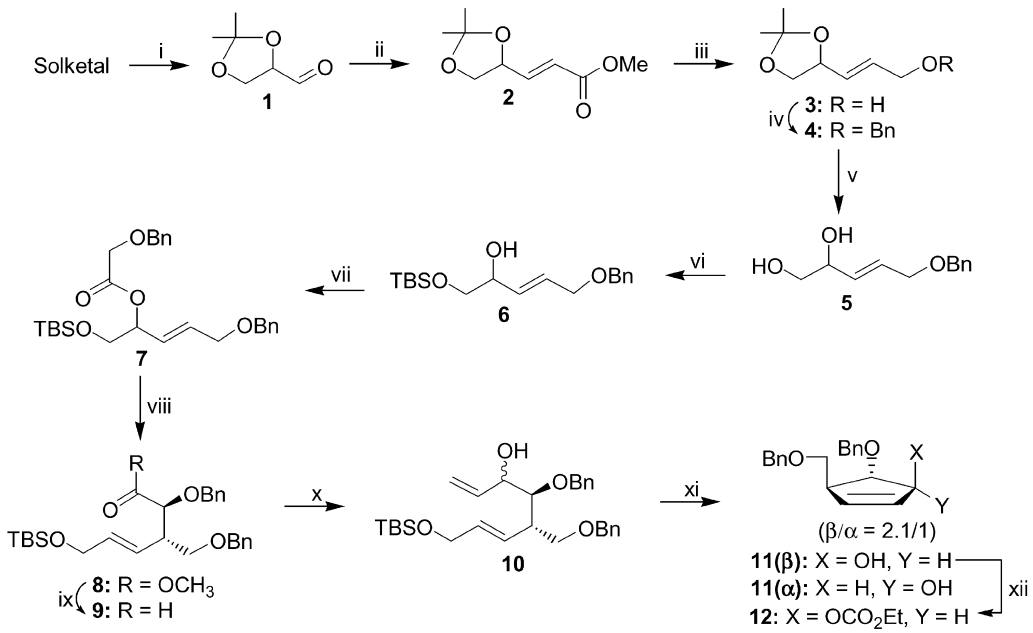


Scheme 1. *Reagents*: (i) PCC, CH_2Cl_2, 4 MS, rt, 5 h, 80%; (ii) $(MeO)_2POCH_2CO_2Me$, NaH, DME, rt, 2 h, 79%; (iii) DIBALH, CH_2Cl_2, −78°C, 2 h, 92%; (iv) BnBr, NaH, THF, overnight, rt, 90%; (v) 2N HCl, rt, 2 h, 95%; (vi) TBDMSCl, imidazole, CH_2Cl_2, 0°C, 5 h, 92%; (vii) $BnOCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, rt, 4 h, 83%; (viii) (a) LHMDS, TMSCl/TEA, THF, −78°C, 1 h, then rt, 3 h, (b) CH_3I, Triton-B, MeOH, overnight, rt, 82% in two steps; (ix) DIBALH, CH_2Cl_2, −78°C, 2 h, 96%; (x) vinylMgBr, THF, −78°C, 1 h, 63%; (xi) $Cl_2(Cy_3P)_2RuCHC_6H_5$, benzene, reflux, 1 h, 82%; (xii) $ClCO_2Et$, pyridine, DMAP, rt, overnight, 86%.

chelation-controlled modification of Ireland's ester enolate Claisen rearrangement (LHMDS, TMSCl/TEA) was used to convert the allylic glycolate ester **7** to a γ,δ-unsaturated glycolate,[14] possibly via a chelation-controlled chair-like transition state, to give the crude acid (Fig. 1). The crude acid, which was not purified because of its high polarity, was treated directly with CH_3I, in the presence of Triton-B, which produced the desired product **8** in a highly stereoselective fashion in an 82% two step yield. With the enolate geometry fixed, the selective entry into either of the diastereomeric series would depend only on the geometry of the olefinic linkage. As a result, a notable increase in the diastereoselectivity resulted from the introduction of an α-substituent in the allylic system. A single diastereomer could be obtained in a majority of α-benzyloxy substrates.

The slow addition of DIBALH to a solution of ester **8** in CH_2Cl_2 at −78°C furnished the desired aldehyde **9** in a 96% yield. The aldehyde **9** underwent a carbonyl addition by

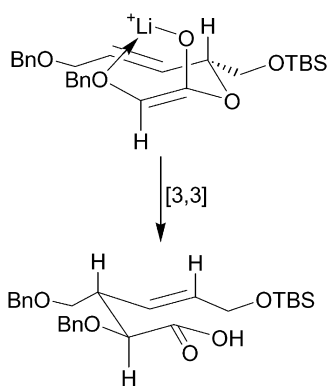


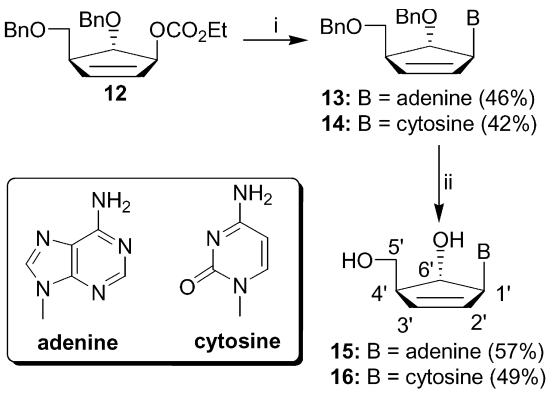
Figure 1. α-chelation controlled transition state.

vinyl magnesium bromide to provide a 2.1:1 mixture of divinyl **10**, as determined by ^1H NMR. The exact stereochemical assignment was performed in the subsequent reaction, because the mixture was difficult to separate at this stage.

The diastereomeric mixture **10** was subjected to the standard RCM[15] conditions using [benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium] to afford the separable cyclopentenols **11(β)** and **11(α)** in a 56 and 26% yield, respectively. A thorough NOE study on the cyclized product, together with the mechanistic rationale for the [3,3]-sigmatropic rearrangement, strongly suggested that the stereochemical assignment of the cyclopentenol **11(β)** and **11(α)** was correct. Indeed, according to the ^1H NMR data, the integral ratio of the crude reaction mixture of compound **10** was almost identical to the ratio of the separated **11(β)** and the more polar **11(α)** isomers (2.1/1).

The stereochemical outcomes could be readily explained in terms of an α-chelation controlled carbonyl addition model.[16] The facile conversion of the hydroxyl group of compound **11(β)** to the palladium substrate **12** was accomplished using ethyl chloroformate in pyridine in an 86% yield.

Palladium catalyzed allylic alkylations[17] are the corner stone in synthetic organic chemistry owing to their highly reliable regio- and stereoselectivity. This methodology was successfully adopted for synthesizing the desired nucleosides (Scheme 2). The adenine and cytosine anion, which was generated by NaH/DMSO in THF/DMSO at 60°C, was successfully condensed with compound **12** using a tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct as the coupling catalyst to give compounds **13** and **14** in a 46



Scheme 2. *Reagents*: (i) adenine and cytosine $Pd_2(dba)_3{\cdot}CHCl_3$, P(*O*-*i*-Pr)$_3$, NaH, THF/DMSO, reflux, overnight; (ii) Na, NH_3/THF, −78°C, 10 min.

and 42% yield, respectively. Although a small amount of the N^7-isomer[18] (6%) of the adenine base was present, it could be readily differentiated [UV(MeOH) λ_{max} 279 nm].

BCl_3 or BBr_3 were used in various reaction conditions to obtain the deprotected 2′,3′-olefinic nucleosides. However, none of the desired products could be obtained under these conditions. Therfore, the Birch-type reaction was used to overcome these problems. Treating compounds **13** and **14** with sodium metal in liquid ammonia at −78°C gave the targeted adenine and cytosine nucleosides **15** and **16** in a 57 and 49% yield, respectively.

The stereochemistry of compound **15** was unambiguously assigned based on the NOE correlations between the proximal hydrogens (H-5′, H-6′vs. H-8) and (H-5′ vs. H-6′), and the structure of compound **16** was also similarly determined.

It should be noted that based on an extensive literature search, the final nucleosides, **15** and **16**, are novel compounds. The antiviral activities of the synthesized compounds were evaluated against the HIV-1, HSV-1, HSV-2, and HCMV, respectively. However, none exhibited any significant antiviral activity up to 100 μM without showing any cytotoxicity.

In summary, a de novo synthetic method for novel 6′(α)-hydroxyl-carbocyclic nucleosides from Solketal was developed. The required relative stereochemistry was successfully elaborated using an α-chelation-controlled [3,3] rearrangement, an α-chelation controlled carbonyl addition and a RCM. Based on this strategy, the optically active syntheses of other 6′-modified carbocyclic nucleosides using different bases are currently underway.

3. Experimental

3.1. General

All chemicals used in this study were of reagent grade and were used as purchased. All moisture-sensitive reactions were performed in an inert atmosphere of either N_2 or Ar using distilled dry solvents. The elemental analyses were performed using an Elemental Analyzer System (Profile HV-3). The NMR spectra were obtained on a bruker 300 Fourier transform spectrometer.

3.1.1. (±)-2,3-(*O*-Isopropylidene)-glyceraldehyde (1). To a cooled (0°C) solution of Solketal **1** (2 g, 15.1 mmol) in dry methylene chloride (50 mL), a 4 Å molecular sieve (7.5 g) and pyridinium chlorochromate (6.5 g, 30.3 mmol) was added with constant stirring. The reaction mixture was stirred for 5 h at room temperature and diluted with diethyl ether. The resulting suspension was filtered through a Florisil pad and washed repeatedly with diethyl ether. The combined extracts were concentrated in vacuo to give compound **1** (1.6 g, 80%) as a liquid, which was used for the subsequent reaction without further purification.

3.1.2. (±)-(4′*E*)-Methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl) acrylate (2). To a suspension of sodium hydride (60% in mineral oil, 307 mg, 7.68 mmol) in distilled DME at 0°C, trimethyl phosphonoacetate (1.24 mL, 7.68 mmol) was added drop wise and with constant stirring for 30 min. The aldehyde **1** (1.0 g, 7.68 mmol) was added to this mixture and stirred for 2 h at room temperature. The solution was neutralized with a saturated ammonium chloride solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and finally evaporated. The residue was chromatographed on a silica gel column (EtOAc/hexane, 1:10) to give **2** (1.13 g, 79%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (dd, *J*=15.0, 6.0 Hz, 1H), 6.04 (dd, *J*=15.0, 1.5 Hz, 1H), 4.68 (m, 1H), 4.18 (m, 1H), 3.75 (s, 3H), 3.63 (m, 1H), 1.48 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.42, 144.98, 121.89, 110.18, 74.86, 68.74, 51.68, 26.39, 25.68.

3.1.3. (*E*)-4,5-(*O*-Isopropylidene)-pent-2-en-1-ol (3). To a cooled solution (−78°C) of compound **2** (10.0 g, 53.7 mmol) in dry CH_2Cl_2 (150 mL), DIBALH (112.7 mL, 1 M solution in hexane) was added slowly. The mixture was stirred for 2 h at the same temperature, and quenched by the slow addition of methanol (112 mL). The solution was stirred for 2 h at rt, and the resulting white solid was filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:2) to give the allylic alcohol **3** (7.8 g, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22–5.81 (m, 1H), 5.62 (dd, *J*=15.2, 6.0 Hz, 1H), 4.51 (ddd, *J*=8, 8, 6 Hz, 1H), 4.24 (m, 2H), 3.52 (t, *J*=8.0 Hz, 2H), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.7, 129.3, s109.7, 72.2, 69.7, 58.4, 27.0, 26.2; Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.58; H, 9.21.

3.1.4. (*E*)-1-Benzyloxy-4,5-(*O*-isopropylidene)-pent-2-ene (4). To a stirred suspension of NaH (2.5 g, 63.5 mmol, 60% oil suspension) in THF (150 mL), a solution of **3** (6.7 g, 42.3 mmol) in dry THF (50 mL) was added slowly, and stirred for 1 h at rt. To this mixture, benzyl bromide (8.68 g, 50.7 mmol) was added, and stirred overnight at rt. The mixture was quenched using a saturated ammonium chloride solution (10 mL), and extracted with EtOAc (200 mL) and water (200 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced

pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **4** (9.45 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (m, 5H), 5.83 (quintet, J=5.5 Hz, 1H), 5.64 (t, J=8.3 Hz, 1H), 4.82 (q, J=10.0 Hz, 1H), 4.57 (dd, J=15.6, 11.8 Hz, 2H), 4.13 (dd, J=6.3, 1.2 Hz, 2H), 4.07 (dd, J=8.0, 6.2 Hz, 1H), 3.57 (t, J=7.9 Hz, 1H), 1.44 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 131.3, 130.8, 128.8, 128.2, 128.1, 109.7, 72.6, 72.5, 69.8, 66.0, 27.2, 26.3; Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.61; H, 8.19.

3.1.5. (±)-1-Benzyloxy-4,5-dihydroxy-pent-2-ene (5). A solution of compound **4** (10 g, 40.27 mmol) in a 2N aqueous HCl solution (150 mL) was stirred for 2 h at rt. The mixture was neutralized by the slow addition of a saturated $NaHCO_3$ solution and diluted with brine (100 mL). The mixture was extracted with EtOAc (150 mL×3), and the combined organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give the diol **5** (7.96 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5H), 5.93–5.86 (dt, J=15.6, 5.5 Hz, 1H), 5.72 (dd, J=15.6, 5.6 Hz, 1H), 4.52 (s, 1H), 4.23 (t, J=7.4 Hz, 2H), 4.04 (d, J=5.5 Hz, 2H), 3.64 (dd, J=11.3, 3.4 Hz, 1H), 3.49 (dd, J=11.3, 7.3 Hz, 1H), 3.10 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 132.5, 129.6, 128.9, 128.3, 128.3, 72.8, 69.2, 66.4, 66.3; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.41; H, 7.68.

3.1.6. (±)-(*E*)-1-Benzyloxy-4-hydroxy-5-(*t*-butyldimethylsilyloxy)-pent-2-ene (6). To a solution of the diol **5** (20.0 g, 96.03 mmol) and imidazole (9.8 g, 0.144 mol) in dry CH_2Cl_2 (300 mL), TBDMSCl (14.47 g, 105.6 mmol) dissolved in anhydrous CH_2Cl_2 (150 mL) was slowly added at −10°C over 30 min. After 30 min at the same temperature, the reaction mixture was quenched using a saturated aqueous $NaHCO_3$ solution (100 mL). The solvent was extracted with CH_2Cl_2 (300 mL) and water (200 mL), and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give compound (28.5 g, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.31 (m, 5H), 5.81 (dt, J=6.0, 5.3 Hz 1H), 5.63 (dd, J=9.6, 8.0 Hz, 1H), 4.54 (s, 2H), 4.22 (m, 1H), 4.07 (d, J=5.0 Hz, 2H), 3.70 (dd, J=10.0, 3.6 Hz, 1H), 3.50 (dd, J=9.5, 8.0 Hz, 1H), 2.6 (br s, 1H), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 131.5, 129.3, 128.7, 128.1, 128.0, 72.6, 70.5, 67.4, 26.2, 18.7, −4.9; Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.89; H, 9.33.

3.1.7. (±)-(*E*)-1-Benzyloxy-4-*O*-(benzyl-glycoloyloxy)-5-(*t*-butyldimethylsilyloxy)-pent-2-ene (7). To a solution of compound **6** (10.6 g, 32.86 mmol) and benzyloxyacetic acid (6.0 g, 36.1 mmol) in dry CH_2Cl_2 (200 mL) DCC (6.78 g, 37.7 mmol) and DMAP (401 mg, 3.28 mmol) was added at 0°C. The reaction mixture was stirred for 4 h at room temperature, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **7** (12.8 g, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.30 (m, 10H), 5.97 (dt, J=15.6, 5.2 Hz, 1H), 5.8 (dd, J=15.6, 6.4 Hz, 1H), 5.55 (dd, J=11.5, 5.7 Hz, 1H), 4.68 (s, 2H), 4.55 (s, 2H), 4.16 (s, 2H), 4.07 (d, J=5.1 Hz, 2H), 3.75 (d, J=5.6 Hz, 2H), 0.92 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 138.6, 137.6, 132.7, 128.9, 128.5, 128.4, 128.3, 128.1, 127.5, 73.7, 73.0, 72.0, 67.6, 66.7, 65.0, 26.3, 18.7, −4.9; Anal. Calcd for $C_{27}H_{38}O_5Si$: C, 68.90; H, 8.14. Found: C, 68.79; H, 8.26.

3.1.8. (±)-(2*S*,3*S*)-2-Benzyloxy-3-benzyloxymethyl-6-(*t*-butyldimethylsilyloxy)-hex-4-enoic acid methyl ester (8). To a cooled (−78°C) solution of 1 M lithium bis(trimethylaily) amide in THF (46.4 mL, 46.4 mmol), a solution of compound **7** (5.5 g, 11.68 mmol) and trimethylsilyl chloride/triethylamine (1/1 v/v, 30.4 mL) in dry THF (200 mL) was slowly added. After stirring for 30 min at the same temperature, the reaction mixture was warmed to rt and stirred for 2 h, and then quenched with a 1N NaOH solution (200 mL) in an ice bath. The resulting mixture was then stirred for 10 min at room temperature, and acidified to pH 4–5 using a 2N HCl solution. The mixture was extracted with EtOAc (300 mL) and water (300 mL). The aqueous layer was extracted twice with EtOAc (200 mL), and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated under vacuum to give a crude acid. Without further purification, the crude acid was dissolved in THF (150 mL) and titrated with Triton-B (40% in methanol) using phenolphthalein as an indicator. After the solution turned violet, it was stirred at rt for 1 h, and CH_3I (2.88 mL, 46.4 mmol) was slowly added. The resulting mixture was stirred overnight at rt. It was then diluted with hexane (150 mL), and filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give the methyl ester **8** (4.6 g, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.28 (m, 10H), 5.70 (m, 2H), 4.84 (d, J=11.5 Hz, 1H), 4.53 (d, J=11.9 Hz, 1H), 4.47 (d, J=11.9 Hz, 1H), 4.39 (m, 2H), 4.16 (s, 2H), 3.74 (s, 3H), 3.65 (t, J=9.3 Hz, 1H), 3.50 (dd, J=9.0, 5.1 Hz, 1H), 2.98 (m, 1H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 138.7, 138.3, 134.0, 128.7, 128.4, 128.1, 128.0, 125.9, 73.4, 73.3, 70.3, 64.2, 52.1, 46.4, 26.4, 18.8, −4.7; Anal. Calcd for $C_{28}H_{40}O_5Si$: C, 69.38; H, 8.32. Found: C, 69.01; H, 8.44.

3.1.9. (±)-(2*S*,3*S*)-2-Benzyloxy-3-benzyloxymethyl-6-(*t*-butyldimethylsilyloxy)-hex-4-enal (9). To a solution of compound **8** (15.2 g, 31.3 mmol) in anhydrous CH_2Cl_2 (62 mL), a DIBALH solution (34.5 mL, 1 M solution in CH_2Cl_2) was slowly added at −78°C. The reaction mixture was stirred for 2 h at the same temperature, quenched by the addition of methanol (34.5 mL), and stirred at rt for 2 h. The resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give the aldehyde **9** (13.6 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.73 (s, 1H), 7.38–7.31 (m, 10H), 5.71 (m, 2H), 4.77 (d, J=11.7 Hz, 1H), 4.56–4.47 (m, 3H), 4.15–4.10 (m, 3H), 3.62–3.52 (m, 2H), 2.97 (m, 1H), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 204.21, 138.47, 138.01, 134.21, 128.83, 128.80, 128.34, 128.09, 125.18, 83.57, 73.53, 73.45, 69.93, 63.88, 45.30, 26.36, 18.80, −4.73; Anal. Calcd for $C_{27}H_{38}O_4Si$: C, 71.32; H, 8.42. Found: C, 70.97; H, 8.27.

3.1.10. (±)-(3*S*,4*S*,5*S*)-3-Hydroxy-4-benzyloxy-5-benzyloxymethyl-8-(*t*-butyldimethylsilyloxy)-1,6-octadiene and (±)-(3*R*,4*S*,5*S*)-3-hydroxy-4-benzyloxy-5-benzyloxymethyl-8-(*t*-butyldimethylsilyloxy)-1,6-octadiene (10). To a solution of compound **9** (5.4 g, 11.87 mmol) in anhydrous THF vinyl magnesium bromide (14.2 mL, 1 M solution in THF) was slowly added at −78°C and stirred for 1 h. The mixture was quenched with a saturated ammonium chloride solution (10 mL), and elevated to room temperature. The mixture was extracted with EtOAc (200 mL) and water (200 mL), washed with brine, dried over anhydrous $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:7) to give a diastereomeric mixture of compound **10** (3.6 g, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.31 (m, 10H), 6.02–5.74 (m, 3H), 5.34–5.21 (m, 2H), 4.68–4.17 (m, 6H), 3.72–3.47 (m, 3H), 2.97–2.85 (m, 1H), 0.93 (s, 9H), 0.09 (s, 6H); Anal. Calcd for $C_{29}H_{42}O_4Si$: C, 72.15; H, 8.77. Found: C, 72.47; H, 8.60.

3.1.11. (±)-(1*S*,4*S*,6*S*)-4-Benzyloxymethyl-6-benzyloxy-cyclopent-2-en-1-ol (11(β)); and (±)-(1*R*,4*S*,6*S*)-4-benzyloxymethyl-6-benzyloxy-cyclopent-2-en-1-ol (11(α). To a solution of Grubbs catalyst (733 mg, 0.89 mmol) in anhydrous benzene (5 mL), the starting material **10** (4.3 g, 8.9 mmol) in anhydrous benzene (5 mL) was slowly added. The mixture was refluxed for 1 h, and cooled to room temperature. The solvent was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give the cyclopentenol **11(β)** (1.55 g, 56%) and the more polar **11(α)** (718 mg, 26%) as colorless oils: **11(β)**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.23 (m, 10H), 6.03 (d, *J*=6.0 Hz, 1H), 5.83 (dd, *J*=6.3, 3.0 Hz, 1H), 4.83 (d, *J*=11.7 Hz, 1H), 4.55 (d, *J*=11.7 Hz, 1H), 4.52 (s, 2H), 4.46–4.40 (m, 1H), 4.01 (dd, *J*=7.5, 2.1 Hz, 1H), 3.66 (dd, *J*=9.3, 3.0 Hz, 1H), 3.59 (s, 1H), 3.56 (s, 1H), 3.44 (dd, *J*=9.3, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 138.39, 137.30, 133.72, 133.30, 128.21, 128.13, 127.62, 127.52, 127.33, 77.83, 73.24, 71.56, 71.27, 66.27, 46.39; Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.58; H, 7.31. **11(α)**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.25 (m, 10H), 5.98 (dd, *J*=6.0, 4.5 Hz, 1H), 5.80 (m, 1H), 4.85 (br s, 1H), 4.68 (s, 2H), 4.60 (s, 2H), 4.01 (dd, *J*=6.9, 4.8 Hz, 1H), 3.75 (dd, *J*=14.4, 5.1 Hz, 1H), 3.48 (dd, *J*=9.0, 7.5 Hz, 1H), 3.18 (m, 1H), 1.8 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.46, 138.38, 134.73, 132.70, 128.37, 128.29, 127.59, 127.55, 127.45, 87.82, 81.05, 73.25, 72.41, 70.00, 46.66; Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.59; H, 7.22.

3.1.12. (±)-(1*S*,4*S*,6*S*)-1-Ethoxycarbonyloxy-4-benzyloxymethyl-6-benzyloxy-cyclopent-2-ene (12). To a solution of compound **11(β)** (2.6 g, 8.37 mmol) and DMAP (101 mg, 0.83 mmol) in anhydrous pyridine (10 mL), ethyl chloroformate (1.36 g, 12.5 mmol) was slowly added. The mixture was stirred overnight at rt, and quenched with a saturated $NaHCO_3$ solution. The solvent was concentrated under vacuum, and the residue was extracted with EtOAc (10 mL) and water (100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:8) to give the cyclopentene **12** (2.7 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.23 (m, 10H), 6.26 (dd, *J*=6.0, 2.7 Hz, 1H), 5.92 (dd, *J*=6.3, 1.8 Hz, 1H), 4.47 (dd, *J*=5.4, 2.4 Hz, 1H), 4.66 (dd, *J*=15.0, 12.3 Hz, 2H), 4.48 (s, 2H), 4.16–4.08 (m, 3H), 3.87 (dd, *J*=8.7, 6.0 Hz, 1H), 3.52 (t, *J*=8.7 Hz, 1H), 3.02 (m, 1H), 1.25 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.76, 140.15, 138.37, 138.15, 128.19, 128.15, 127.62, 127.50, 127.41, 127.36, 127.32, 78.19, 77.79, 73.17, 72.64, 71.48, 63.75, 46.65, 14.13; Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.14; H, 6.77.

3.1.13. (±)-(1′*S*,4′*S*,6′*S*)-9-[4-Benzyloxymethyl-6-benzyloxy-cyclopent-2-en-1-yl] adenine (13). To a stirred pure NaH (17.8 mg, 0.74 mmol) solution in anhydrous DMSO, adenine (100 mg, 0.74 mmol) was added. The reaction mixture was stirred for 45 min at 45–55°C to prepare the sodium salt of adenine, and was then cooled to room temperature. Simultaneously, P(*O*-*i*-Pr)$_3$ (0.053 mL, 0.12 mmol) was added to a solution of $Pd_2(dba)_3.CHCl_3$ (2.53 mg, 1.37 μmol) in anhydrous THF (2.0 mL), which was stirred for 45 min. To the adenine solution in DMSO, a catalyst solution of THF and **12** (183.5 mg, 0.48 mmol) dissolved in anhydrous THF (2 mL) was sequentially added. The reaction mixture was gently refluxed overnight and quenched with water (1.5 mL). The reaction solvent was removed under vacuum. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:10) to give compound **13** (94.3 mg, 46%) as a white solid. mp 186–189°C; UV (MeOH) λ_{max} 261 nm: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (s, 1H), 8.00 (s, 1H), 7.34–7.21 (m, 10H), 6.45 (s, 1H), 6.14 (dd, *J*=5.4, 2.7 Hz, 1H), 5.79 (d, *J*=7.2 Hz, 1H), 5.50 (s, 1H), 4.66 (dd, *J*=15.6, 12.0 Hz, 2H), 4.57 (dd, *J*=6.3, 2.4 Hz, 1H), 4.17 (d, *J*=11.7 Hz, 1H), 4.09 (d, *J*=11.4 Hz, 1H), 3.46 (t, *J*=9.0 Hz, 1H), 3.22 (t. *J*=7.2 Hz, 1H), 2.96 (q, *J*=6.9 Hz, 1H), 2.83 (br s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.40, 152.87, 150.18, 141.21, 138.28, 137.66, 136.98, 133.34, 128.58, 128.50, 128.22, 127.76, 127.67, 127.53, 127.42, 81.196, 73.43, 72.321, 65.82, 57.55, 45.98; Anal. calcd for $C_{25}H_{25}N_5O_2$: C, 70.24; H, 5.89; N, 16.38. Found: C, 70.44; H, 5.79; N, 16.51.

3.1.14. (±)-(1′*S*,4′*S*,6′*S*)-1-[4-Benzyloxymethyl-6-benzyloxy-cyclopent-2-en-1-yl] cytosine (14). The cytosine derivative **14** was synthesized using the same procedure described for synthesizing compound **13**; yield 42%; mp 182–185°C; UV (MeOH) λ_{max} 272 nm: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.24 (m, 11H), 7.07 (br s, 2H), 6.46 (d, *J*=6.8 Hz, 1H), 5.98 (m, 1H), 5.73 (d, *J*=8.1 Hz 1H), 5.59 (d, *J*=7.5 Hz, 1H), 4.67 (d, *J*=12.0 Hz, 1H), 4.59 (d, *J*=12.0 Hz, 1H), 4.45 (d, *J*=3.9 Hz, 1H), 4.32 (s, 2H), 3.42–3.25 (m, 4H), 2.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.1, 156.6, 143.7, 139.6, 139.2, 137.5, 134.8, 129.1, 129.0, 128.3, 128.2, 128.1, 128.0, 93.8, 81.7, 73.3, 71.9, 66.2, 59.6, 45.3; Anal. calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.69; H, 6.33; N, 10.51.

3.1.15. (±)-(1′*S*,4′*S*,6′*S*)-9-[4-Hydroxymethyl-6-hydroxy-cyclopent-2-en-1-yl] adenine (15). To a solution of compound **13** (80 mg, 0.187 mmol) in anhydrous THF (1 mL) at −78°C, anhydrous ammonia gas was bubbled until the total volume of the solution reached 4 mL. To this mixture, a small portion of Na metal was added until a blue color persisted for 5 min. The mixture was quenched using a few drops of methanol and then warmed to room temperature. The residue was dissolved in 3 mL of methanol and neutralized with AcOH. The mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:6) to give compound **15** (26 mg, 57%) as a white solid: mp 189–190°C; UV (H_2O) λ_{max} 260 nm: ^1H NMR (DMSO-d_6, 300 MHz) δ 8.09 (s, 1H), 7.97 (s, 1H), 7.30 (br s, 1H), 6.31 (s, 1H), 6.01 (d, J=3.0 Hz, 1H), 5.51 (d, J=8.1 Hz, 1H), 4.62 (d, J=3.6 Hz, 1H), 3.37 (t, J=7.5 Hz, 1H), 2.99 (q, J=7.8 Hz, 1H), 2.61 (quint, J=6.9 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.9, 152.7, 150.2, 142.0, 139.9, 132.0, 119.8, 74.1, 59.4, 57.8, 48.6; Anal. Calcd for $C_{11}H_{13}O_5N_2$: C, 53.43; H, 5.30, N, 28.32. Found: C, 53.71; H, 5.21; N, 28.49.

3.1.16. (±)-(1′*S*,4′*S*,6′*S*)-1-[4-Hydroxymethyl-6-hydroxy-cyclopent-2-en-1-yl] cytosine (16). The cytosine derivative **16** was synthesized using same reaction condition used for synthesizing compound **15**; yield 49%; mp 168–171°C; UV (H_2O) λ_{max} 271 nm: ^1H NMR (MeOH-d_4, 300 MHz) δ 7.61 (d, J=7.4 Hz, 1H), 6.38 (dd, J=2.9, 1.4 Hz, 1H), 5.97 (dd, J=5.4, 2.5 H, 1H), 5.85 (d, J=7.4 Hz, 1H), 5.65 (s, 1H), 4.79 (dd, J=6.2, 2.3 Hz, 1H), 3.61 (dd, J=11.4, 3.9 Hz, 1H), 3.47 (dd, J=11.0, 6.98, 1H), 2.68 (quint, J=6.9 Hz, 1H); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 166.4, 158.6, 144.6, 139.6, 131.9, 94.3, 74.2, 61.6, 57.9; Anal. calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.69; H, 6.03; N, 18.51.

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