Stereoselective Synthesis of rac-4'-Ethynyl-2'-deoxy- and 4'-Ethynyl-2',3'-dideoxy-2',3'-didehydronucleoside Analogues

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Abstract: Synthesis of a racemic 4'-ethynyl-2'-deoxyribose intermediate using stereoselective chelation control is presented. This intermediate is further transformed to 4'-ethynyl-2'-deoxy- and 4'-ethynyl-2',3'-dideoxy-2',3'-didehydronucleoside analogues.

Key words: HIV, nucleosides, stereoselective synthesis, carbohydrates, chelation control

Highly active antiretroviral therapy (HAART) using two or more HIV reverse transcriptase inhibitors in combination with other anti-HIV drugs has dramatically improved the quality of life and survival of patients infected with HIV.1 In the discovery of new HAART agents, viral resistance remains a challenge along with the necessity for improved safety and tolerability. The presence of AZT in anti-HIV therapy is believed to block or hinder what is otherwise an easy pathway to resistance (– K65R +/- M184V) as observed from clinical findings with and without inclusion of AZT.2 However, due to long-term toxicity concerns associated with the use of AZT in HAART,3 discovery of a nontoxic nucleoside analogue exhibiting a resistance profile similar to AZT is desirable. One common structural feature found in recent anti-HIV nucleoside analogues is a 4'-ethynyl on the ribose moiety (Figure 1). The 4'-ethynyl group affords a good combination of potency and low cytotoxicity relative to other structural changes investigated at the 4'-position.4

For example, compounds 1–3 in Figure 1 all show potent, sub-1μM anti-HIV activity and CC50 >100 μM.5–n

Existing synthetic methods for introduction of the 4'-ethynyl group are limited by lack of stereoselectivity, and long synthetic sequences.5 The most often used method involves Cannizzaro introduction of geminal hydroxymethyl groups at C-4' followed by selective protection of one primary alcohol over the other. This approach is low yielding and lengthy. We reasoned that synthesis of 4'-ethynylribose analogues could be simplified by introduction of the 4'-group using chelation-controlled addition onto an acyclic ketone bearing an α-alkoxy protected alcohol.6 Ring closure via reduction of the ester to an aldehyde and cyclization of the tertiary alcohol onto the aldehyde could then provide a suitable furanose for introduction of the nucleoside base (Scheme 1).7 Synthesis of single enantiomer nucleosides, although not demonstrated here, is feasible when starting with enantiomerically pure γ-keto esters. This paper describes execution of this strategy for synthesis of (+)-1, (+)-2, and (+)-3.

Synthesis of γ-keto ester 8 involved a five-step sequence depicted in Scheme 2. Alkylation of the lithium enolate of
isopropyl acetate with freshly distilled acrolein resulted in an 88% crude yield of β-hydroxy ester 5. Protection as the MOM ether using dimethoxymethane and BF$_3$·OEt$_2$ was followed by filtration through Celite giving an 85% crude yield of allylic ether 6. Diolysis using catalytic OsO$_4$, NMO afforded the corresponding diol which was selectively protected at the primary alcohol using TBDMSCl to afford an 82% yield of 7 as a 3:1 mixture of diastereomers. Mild oxidation of the secondary alcohol using TPAP/NMO afforded a 92% yield of keto ester 8 as a yellow oil.

Chelation-controlled addition of ethynylmagnesium bromide to 8 afforded a single diastereomer of tertiary alcohol, 9, in 98% yield. The stereochemistry of this product was predicted from a closely related reaction found in the literature and suggested by a chelation control model (Figure 2). The stereochemical assignment of 9 was established only after the desired final nucleoside products had been synthesized and their stereochemical assignments confirmed by NOE experiments and comparison to literature NMR data.

![Figure 2 Chelation control model for the formation of 9](image)

From 9, ring-closure of the resulting tertiary alcohol was accomplished via DIBAL reduction of the isopropyl ester to the corresponding aldehyde followed by spontaneous cyclization. Furanose 10 was isolated in 82% yield following silica gel chromatography as a 1:1 mixture of anomers. Final preparation of the ribose coupling partner 11 was accomplished by acetylation of the 1'-OH group in 93% yield affording a 1:3 mixture of α:β anomers. The overall yield of the eight-step procedure to 11 is 42% (Scheme 3).

Thymidine nucleosides (±)-1 and (±)-2 share a common route of preparation as depicted in Scheme 4. Silyl Hilbert–Johnson coupling of silylated thymine with 11 catalyzed by TMSOTf proceeded smoothly to afford a 98% yield of 12 as a 1:1 anemic mixture. Separation and isolation of the β-anomer at this stage was not straightforward but protecting group manipulation followed by anomer separation at intermediate 14 proved successful. Deprotection of the MOM and silyl ether groups was accomplished using anhydrous HCl in MeOH to afford 13 in 85% yield. Silyl protection at the 5'-OH of 13 gave 14. A portion of 14 (1:1 mixture of anomers) was purified via silica gel chromatography to afford pure 14-β in 19% yield along with a set of fractions containing 14-α:β (9:1 α:β mixture) in 30% yield. Deprotection of 14-β using NH$_4$F in MeOH afforded (±)-1 in 33% yield. Another portion of 14-β was converted to the secondary mesylate 15-β under standard conditions. It was discovered that when 15-β was treated with TBAF in refluxing THF, simultaneous elimination of the mesylate and deprotection of the silyl ether took place to afford (±)-2 in 45% yield.

The synthesis of (±)-3 begins with silyl Hilbert–Johnson coupling of 11 with N'-benzoyl-5-fluorocytosine to afford 5-fluorocytidine 16 as a mixture of anomers (Scheme 5). Purification of the mixture was accomplished via silica gel chromatography to afford 16-β in 31% yield. Deprotection was conducted as in the thymidine case to afford (±)-3 in 41% yield. In addition to NOE experiments performed on the final nucleosides which unambiguously confirmed the stereochemistry at the anomeric center, the proton NMRs of racemic nucleosides 1–3 matched the lit-
erature NMR data confirming the stereochemical assignment of 9 and subsequent intermediates.

We have demonstrated an efficient, novel method for the synthesis of 4¢-ethynyl-substituted nucleoside analogues. Replacement of ethynylmagnesium bromide with other Grignard reagents is expected to offer entry into additional 4¢-substituted carbohydrates and nucleoside analogues. Furthermore, the selection of chiral γ-keto ester starting materials such as (+)-510a and (–)-510b offer entry into either enantiomer of 4¢-substituted carbohydrates and nucleoside analogues. When combined with methods to generate enantiomerically pure γ-keto esters, the strategy described herein represents a highly versatile approach to this important class of compounds.

NMR spectroscopy was performed on a Jeol EXC300 spectrometer, operating at 300 MHz (1H NMR) and 75 MHz (13C NMR). NMR spectra were obtained as CDCl3 solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or DMSO-d6 (2.50 ppm and 39.51 ppm) or CD3OD (3.4 ppm and 4.8 ppm, and 49.3 ppm), or internal tetramethylsilane (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

Melting points were obtained on an Electrothermal 9100 melting point apparatus. Mass spectrometry was carried out on a Waters/Micromass ZQ2000 instrument. Elemental analyses were obtained from Elemental Microanalysis, Okehampton, UK.

Isopropyl 3-Hydroxypent-4-enoate (5)

To a solution of i-Pr2NH (153 mL, 1.09 mol) in THF (750 mL) at –78 °C was added n-BuLi (680 mL, 1.6 M in hexanes, 1.09 mol) over 20 min. After stirring for 45 min, isopropyl acetate (115 mL, 0.980 mol) was added over 10 min. After stirring a further 45 min, a solution of freshly distilled acrolein (65.6 mL, 0.980 mol) in THF (200 mL) was added over 15 min. The mixture was stirred for 15 min and allowed to self-warm to r.t. and stirred overnight. The mixture was diluted with EtOAc (750 mL) and washed with aq sat. NH4Cl (2 × 100 mL) and brine (2 × 100 mL). The combined organic extracts were dried (MgSO4) and concentrated in vacuo to give 5 (136 g, 88% crude yield) as a brown oil which was used as such in the next reaction. An analytical sample was obtained by silica gel column chromatography eluting with 4:1 hexane–EtOAc; Rf = 0.44 (4:1 hexane–EtOAc).

Scheme 4  Reagents and conditions: (i) 1. thymine, N,O-bis(trimethylsilyl)acetamide, MeCN, reflux, 1 h, 2. 11, TMSOTf, r.t., 3 h, 98%; (ii) 1. AcCl, MeOH, 22 h, 2. NaOMe, MeOH, 85%; (iii) TBDMSCl, pyridine; (iv) anomeric separation, 19% pure 14-β; (v) NH4F, MeOH, 33%; (vi) MsCl, Et3N, CH2Cl2, 5 °C → r.t., 84%; (vii) TBAF, THF, reflux, 2 d, 45%.

Scheme 5  Reagents and conditions: (i) N-benzoyl 5-fluorocytosine, N,O-bis(trimethylsilyl)acetamide, MeCN, reflux, 0.5 h, 2. 11, TMSOTf, r.t., 2 h, 87%; (ii) separation of anomers, 31% pure 16-β, (iii) 1. AcCl, MeOH, 5 d, 2. NaOMe, MeOH, 41%.
H NMR (300 MHz, CDCl3): δ = 5.86 (ddd, J = 5.5, 10.4, 17.3 Hz, 1 H), 5.30 (dt, J = 1.4, 17.3 Hz, 1 H), 5.13 (dt, J = 1.4, 10.4 Hz, 1 H), 5.00–5.08 (m, 1 H), 4.47–4.54 (m, 1 H), 3.06 (d, J = 4.0 Hz, OH, 1 H), 2.56 (dd, J = 4.1, 16.2 Hz, 1 H), 2.48 (dd, J = 8.0, 16.2 Hz, 1 H), 1.25 (d, J = 6.3 Hz, 6 H).

13C NMR (75 MHz, CDCl3): δ = 171.9, 138.9, 115.4, 69.0, 68.4, 41.5, 21.9 (2 C).

Isopropyl 3-(Methoxymethoxy)pent-4-enoate (6)

To a mixture of 5 (207 g, 1.31 mol), CH2Cl2 (1.75 L), dimethoxymethane (1.25 L), and 4 Å powdered MS (410 g) at 5 °C, was added BF3·OEt2 (249 mL, 2.0 mol) over 30 min. After 30 min, the mixture was warmed to 10 °C, stirred for 3 h, then Na2CO3 (250 g) was added over 25 min. After stirring for a further 25 min, the mixture was filtered through Celite, washed with sat. aq Na2CO3 (2 × 300 mL) and dried (MgSO4). Concentration in vacuo gave 6 (223 g, 85%) as a yellow oil which was used directly in the next reaction. An analytical sample was obtained by silica gel column chromatography eluting with CH2Cl2: Rf = 0.41 (CH2Cl2).

1H NMR (300 MHz, CDCl3): δ = 5.65–5.76 (dd, J = 7.7, 10.4, 17.9 Hz, 1 H), 5.29 (m, 1 H), 5.20 (m, 1 H), 4.96–5.07 (sept, J = 6.3 Hz, 1 H), 4.67 (d, J = 6.6 Hz, 1 H), 4.54 (d, J = 6.6 Hz, 1 H), 4.42–4.50 (m, 1 H), 3.33 (s, 3 H), 2.60 (dd, J = 8.2, 15.0 Hz, 1 H), 2.45 (dd, J = 5.5, 15.0 Hz, 1 H), 1.20 (d, J = 6.3 Hz, 6 H).

13C NMR (75 MHz, CDCl3): δ = 170.3, 136.9, 119.1, 94.1, 74.0, 68.0, 55.6, 41.4, 21.9 (2 C).

Isopropyl 5-([tert-Butyl(dimethyl)silyl]oxy)-3-(methoxymethylene)pentan-4-one (7)

To a solution of 6 (409 g, 2.02 mol) in acetone (2.5 L) and H2O (500 mL) was added N-methylmorpholine N-oxide (273 g, 2.53 mol) and OsO4 (4.0 g, 16 mmol). The mixture was stirred at r.t. for 24 h, diluted with brine (750 mL) and aq 1 M Na2SO4 (750 mL), and then extracted with EtOAc (3 × 2 L). The organics were combined, dried (MgSO4) and concentrated in vacuo to give the crude diol as a yellow oil which was used directly in the next reaction. An analytical sample was obtained by silica gel column chromatography eluting with EtOAc: Rf = 0.61 (4:1 hexane–EtOAc).

1H NMR (300 MHz, CDCl3): δ = 4.97 (sept, J = 6.3 Hz, 1 H), 4.67 (d, J = 6.6 Hz, 1 H), 4.62 (d, J = 6.6 Hz, 1 H), 4.55 (dd, J = 4.7, 6.9 Hz, 1 H), 4.48 (d, J = 6.9 Hz, 2 H), 2.79 (dd, J = 4.7, 16.2 Hz, 1 H), 2.70 (dd, J = 6.9, 16.2 Hz, 1 H), 1.18 (d, J = 6.3 Hz, 6 H), 0.88 (s, 9 H), 0.06 (s, 6 H).

13C NMR (75 MHz, CDCl3): δ = 207.9, 169.6, 97.1, 77.0, 68.5, 68.0, 56.1, 37.4, 25.8 (3 C), 21.8 (2 C), 18.4–5.4 (2 C).

Isopropyl 5-([tert-Butyl(dimethyl)silyl]oxy)-2-deoxy-4-ethyl-3-(methoxymethylene)ethyl
diydro-3H-pent-2-en-2-one (9)

To a solution of 8 (39 g, 0.11 mol) in THF (650 mL) at −78 °C, was added 0.5 M ethynylmagnesium bromide in Et2O (236 mL, 0.12 mol) over 25 min. The mixture was stirred for 30 min at −78 °C, then allowed to warm to r.t. over 30 min and stirred for a further period of 2 h. The reaction was quenched with 1 M aq citric acid (500 mL) and extracted with EtOAc (2 × 500 mL). The combined organic extracts were dried (MgSO4) and concentrated in vacuo to give 9 (41.1 g, 98%) as a yellow oil which was used directly in the next reaction. An analytical sample was obtained by silica gel column chromatography eluting with CH2Cl2: Rf = 0.71 (4:1 hexane–EtOAc).

1H NMR (300 MHz, CDCl3): δ = 4.97 (sept, J = 6.3 Hz, 1 H), 4.71 (d, J = 6.6 Hz, 1 H), 4.68 (d, J = 6.6 Hz, 1 H), 4.11 (dd, J = 3.6, 8.0 Hz, 1 H), 3.82 (d, J = 9.8 Hz, 1 H), 3.71 (d, J = 9.8 Hz, 1 H), 3.33 (s, 3 H), 3.29 (s, 1 H, OH), 2.92 (dd, J = 3.6, 16.2 Hz, 1 H), 2.64 (dd, J = 8.0, 16.2 Hz, 1 H), 2.41 (s, 1 H, CH2), 1.21 (d, J = 6.3 Hz, 6 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

13C NMR (75 MHz, CDCl3): δ = 171.6, 97.9, 82.5, 77.9, 72.8, 68.1, 66.7, 56.2, 37.5, 25.9 (3 C), 21.9 (2 C), 18.4–5.36 (2 C).

5-O-([tert-Butyl(dimethyl)silyl]oxy)-2-deoxy-4-ethyl-3-O-(methoxymethylene)ethyl
diydro-3H-pent-2-en-2-one (10)

To a solution of 9 (41 g, 0.11 mol) in CH2Cl2 (650 mL) at −78 °C, was added 1.0 M DIBAL (220 mL, 0.22 mol) and the mixture was stirred for 1.5 h. The reaction was quenched with MeOH (100 mL), warmed to −10 °C, and diluted with aq sodium potassium tartrate (200 mL). After stirring for 10 min, the mixture was filtered through Celite and extracted with CH2Cl2 (2 × 1 L). The combined organic extracts were dried (MgSO4), concentrated in vacuo, and the residue purified by flash silica gel chromatography eluting with 1:1 hexane–EtOAc to give 10 (28.1 g, 81%) as a colorless oil (1:1 mixture of anomers); Rf = 0.31 (4:1 hexane–EtOAc).

1H NMR (300 MHz, CDCl3): δ = 5.47 and 5.39 (2 dd, J = 3.6, 3.6, 7.1 and 1.6, 4.1, 8.5 Hz, 1 H), 4.61–4.76 (m, 2 H), 4.46 and 4.32 (t and dd, J = 7.4 and 3.0, 6.3 Hz, 1 H), 3.52–3.75 (m, 3 H), 3.35 and 3.34 (2 s, 3 H), 2.56 and 2.55 (2 s, 1 H), 2.02–2.38 (m, 2 H), 0.87 and 0.83 (2 s, 9 H), 0.07 and 0.06 (2 s, 3 H).

13C NMR (75 MHz, CDCl3): δ = 99.4, 97.6, 96.2, 95.9, 83.7, 83.2, 81.8, 80.7, 77.4, 76.9, 76.1, 67.1, 67.0, 55.7, 40.9, 40.3, 25.9, 25.8 (3 C), 18.4, 18.3, –5.4, –5.5 (2 C).
1-O-Acetyl-5-O-[[(tert-butyl(dimethyl)silyl)-2-deoxy-4-ethyl-3-O-(methoxymethyl)ethyloxy]propenofuranosyl]-5-methylpyrimidine-2,4(1H,3H)-dione (11-β)

To a solution of 10 (28 g, 89 mmol) in CH₂Cl₂ (400 mL) at 0 °C, was added 4N HCl/MeOH solution (400 mL) over 3 min. The mixture was stirred for 30 min, allowed to warm to r.t. and washed with 1 M aq citric acid (200 mL). The combined organic extracts was dried (MgSO₄) and concentrated in vacuo to give 11 (29 g, 93%) as a colorless oil (1:3 mixture of α:β anomers). An analytical sample of each was obtained by silica gel chromatography eluting with 4:1 hexane–EtOAc.

11-β

R₁ = 0.51 (4:1 hexane–EtOAc).

1H NMR (300 MHz, CDCl₃): δ = 6.27–6.29 (m, 1 H), 4.76 (d, J = 6.9 Hz, 1 H), 4.69 (d, 6.9 Hz, 1 H), 4.37 (d, J = 4.7, 7.7 Hz, 1 H), 2.37 (s, 3 H), 2.50–2.60 (m, 2 H), 2.10 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 169.9, 96.5, 96.3, 83.8, 80.7, 76.2, 75.2, 65.7, 55.7, 38.0, 25.9 (3 C), 21.3, 18.4, –5.26, –5.46.

11-α

R₁ = 0.42 (4:1 hexane–EtOAc).

1H NMR (300 MHz, CDCl₃): δ = 6.22 (dd, J = 2.5, 5.8 Hz, 1 H), 4.74 (d, J = 6.9 Hz, 1 H), 4.68 (d, 6.9 Hz, 1 H), 4.37 (d, J = 4.7, 7.7 Hz, 1 H), 2.37 (s, 3 H), 2.50–2.60 (m, 2 H), 2.18 (ddd, J = 2.5, 4.4, 14.0 Hz, 1 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 170.5, 97.9, 96.2, 84.6, 80.6, 76.3, 66.8, 55.7, 38.9, 25.9 (3 C), 21.4, 13.8, –5.26, –5.5.

1-[(5-O-[[(tert-Butyl(dimethyl)silyl)-2-deoxy-4-ethyl-3-O-(methoxymethyl)ethyloxy]propenofuranosyl]-5-methylpyrimidine-2,4(1H,3H)-dione (12)

A suspension of thymine (10.5 g, 84.0 mmol) and NO-bis(trimethylsilyl)acetamide (41.3 mL, 168 mmol) in MeCN (300 mL) was heated at reflux for 1 h. The mixture was cooled to r.t. and 11 (15 g, 42 mmol) was added followed by TMSOTf (22.7 mL, 125 mmol). The mixture was stirred at r.t. for 3 h, diluted with EtOAc (900 mL) and washed with sat. aq Na₂CO₃ (1 L). The aqueous phase was back-extracted with EtOAc (700 mL) and the organic layers were combined, dried (MgSO₄), and concentrated in vacuo. The residue was further purified by flash chromatography eluting with 1:1 CH₂Cl₂–MeOH to give 12 (17.4 g, 98%) as a cream-colored foam (1:1 mixture of anomers; R₁ = 0.42 (19:1 CH₂Cl₂–MeOH).

1H NMR (300 MHz, CDCl₃): δ = 9.40 and 9.33 (2 br s, NH), 7.72 and 7.33 (2 s, 1 H), 6.37 and 6.21 (2 d, J = 5.2, 14 and 5.2, 6.6 Hz, 1 H), 4.61–4.48 (m, 2 H), 3.84 and 3.84 (2 d, J = 11.3 and 11.3 Hz, 1 H), 3.76 (d, J = 1.4 Hz, 1 H), 3.39 and 3.36 (2 s, 3 H), 2.49–2.86 (m, 2 H), 2.11–2.28 (m, 1 H), 1.89–1.93 (m, 3 H), 0.92 and 0.88 (2 s, 9 H), 0.07–0.11 (m, 6 H).

13C NMR (75 MHz, CDCl₃): δ = 164.2, 163.9, 150.6, 150.4, 136.5, 135.3, 111.2, 110.6, 96.5, 96.3, 83.4, 80.2, 79.5, 77.8, 76.9, 76.2, 75.1, 66.8, 65.4, 55.9, 55.8, 39.1, 38.0, 26.0, 25.9 (3 C), 18.5, 18.3, 12.8, 12.7, –5.26, –5.37, –5.49.

1-(2-Deoxy-4-ethyl-β-erythro-propenofuranosyl)-5-methylpyrimidine-2,4(1H,3H)-dione (14-α)

R₁ = 0.42 (19:1 CH₂Cl₂–MeOH).

1H NMR (300 MHz, CDCl₃): δ = 8.76 (br s, NH), 7.40 (d, J = 1.1 Hz, 1 H), 6.84 (d, J = 5.5 Hz, 1 H), 4.45 (d, J = 11.0 Hz, 1 H), 2.81–2.89 (m, 2 H), 2.15 (dt, J = 4.1, 14.0 Hz, 2 H), 1.92 (d, J = 1.3 Hz, 3 H), 0.90 (s, 9 H), 0.01 (s, 6 H).

13C NMR (75 MHz, CDCl₃): δ = 163.6, 150.2, 135.4, 111.3, 84.9, 84.0, 78.7, 77.3, 71.6, 66.1, 39.5, 26.0 (3 C), 18.5, 12.6, –5.28, –5.31.

1-(2-Deoxy-4-ethyl-β-erythro-propenofuranosyl)-5-methylpyrimidine-2,4(1H,3H)-dione (14-β)

Compound 14-β (55 mg, 0.145 mmol) was placed in a conical sealed tube and dissolved in MeOH (1 mL). A 0.5 M solution of NH₄F in MeOH (1 mL, 0.5 mmol) was added and the tube was sealed and heated at 60 °C for 5 h. The solvent was removed and the residue was purified by preparative HPLC to give (β)-1 (12.4 mg, 33%) as a white solid. The 1H NMR (DMSO-d₆) matched with that reported in the literature.

1-[(5-O-[[(tert-Butyl(dimethyl)silyl)-2-deoxy-4-ethyl-3-O-(methylsulfonyl)ethyloxy]propenofuranosyl]-5-methylpyrimidine-2,4(1H,3H)-dione (15-β)

To a solution of 14-β (1.1 g, 3.0 mmol) in CH₂Cl₂ (100 mL) was added Et₃N (50.0 mL, 36 mmol) and MeSOCl (0.24 mL, 3.1 mmol) at 5 °C. After 5 min, the mixture was allowed to warm to r.t. and stirred for 3 h. The mixture was washed with aq NaOH (100 mL) and the organic extracts were combined, dried (MgSO₄), and concentrated in vacuo to give 15-β (1.15 g, 84%) as white foam; R₁ = 0.72 (19:1 CH₂Cl₂–MeOH).
1H NMR (300 MHz, CDCl3): δ = 8.72 (br s, NH), 7.58 (d, J = 1.4 Hz, 1 H), 6.27 (dd, J = 4.4, 6.9 Hz, 1 H), 5.29 (dd, J = 4.4, 6.6 Hz, 1 H), 3.85 (d, J = 11.2 Hz, 1 H), 3.82 (d, J = 11.2 Hz, 1 H), 2.97–3.16 (m, 4 H), 2.84 (s, 1 H), 2.43 (dt, J = 4.4, 14.6 Hz, 1 H), 1.95 (d, J = 3 H, 1 H), 1.94 (s, 9 H), 0.91 (s, 9 H), 0.11 (s, 6 H).

13C NMR (75 MHz, CDCl3): δ = 160.4, 150.2, 135.5, 111.1, 85.7, 85.1, 79.1, 78.3, 78.0, 67.0, 39.5, 38.7, 25.9 (C 3), 18.3, 12.8, –5.3, –5.5.

4- (Benzyloxylino)-1-[5-O-(tert-butyl(dimethyl)silyl)-2-deoxy-4-ethynyl-3-(methoxymethyl)(β-erythro-pentofuranosyl)-5-fluoropyrimidin-2(1H)-one (16β)

A suspension of β-n-Benzylo-5-fluorocytosine (13.0 g, 55.8 mmol) and N,O-bis(trimethylsilyl)acetamide (27.5 mL, 112 mmol) in MeCN (250 mL) was heated at reflux for 0.5 h. The mixture was cooled to r.t. and 11H (14.0 g, 39.1 mmol) was added followed by TMSOTf (141.4 mL, 78.1 mmol). The mixture was stirred at r.t. for 2 h and quenched with sat. aq Na2CO3 (200 mL), and diluted with EtOAc (1 L). The EtOAc layer was washed with brine (500 mL), and dried (MgSO4) and concentrated in vacuo. The residue was purified by flash silica chromatography eluting with 7% MeOH–CH2Cl2 to give (±)-2 (0.26 g, 45%) as a yellow solid; Rf = 0.57 (7% MeOH–CH2Cl2).

1H NMR (300 MHz, DMSO-d6): δ = 11.33 (br s, NH), 7.75 (d, J = 1.1 Hz, 1 H), 6.85 (t, J = 1.7 Hz, 1 H), 6.32 (dd, J = 1.9, 5.8 Hz, 1 H), 6.02 (dd, J = 1.2, 5.8 Hz, 1 H), 5.45 (t, J = 5.8 Hz, OH), 3.53–3.69 (m, 3 H), 1.68 (d, J = 1.1 Hz, 1 H).

13C NMR (75 MHz, DMSO-d6): δ = 164.4, 151.3, 137.3, 136.0, 127.6, 109.5, 89.4, 87.1, 82.0, 77.9, 66.3, 12.7.

MS: m/z = 249.04 [M + H]+.

References


(6) (a) Marco, J. A.; Carda, M.; Gonzalez, F.; Rodriguez, S.; Castillo, E.; Murga, J. *J. Org. Chem.* **1998**, *63*, 698. (b) This reference explains the observed syn addition of ethynylmagnesium bromide by an α-chelate where the oxygen atom alpha to the ketone forms a 5-ring chelate as shown in Figure 2. Ether protecting groups other than MOM are expected to afford good chelation control since the authors in reference 6 report 91:9 syn-selectivity using ethynylmagnesium chloride and a ketone substrate having α-OBn in place of MOM and TBDPS in place of TBDMS.

(7) For another nucleoside example of building functionality into an acyclic intermediate followed by ring-closure, see:

