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Synthesis of a novel uridine analogue and its use in attempts to form new cyclonucleosides using ring-closing metathesis

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One novel nucleoside analogue having a hex-5-enyl group and an allyl group in the 5′-C and 3-N position was synthesized regio- and diastereoselectively from D-glucose in twelve steps. In order to reach a particular conformation of nucleosides the nucleoside formation of restricted cyclonucleoside analogues was studied via Ring-Closing Metathesis.

nucleoside, restrictedconformation, metathesis

1 Introduction

Natural nucleosides and analogues are of great biological importance in metabolic pathways and in antitumoral/antiviral diseases [1–4]. The typical shape of nucleosides has two molecular moieties: D-ribo- or D-2′-deoxyribopentofuranose as the sugar moiety and a purine or pyrimidine aglycone. These two fragments are covalently bonded from N-1 of pyrimidine or N-9 of purine to C-1′ of the glycone in a β-configuration [5]. In order to investigate the conformational preference of nucleoside analogues, the limitation of conformation of a nucleoside or nucleotide is widely used [6–10]. Different conformationally constrained nucleosides have been used and can be classified into three families: bicyclonucleosides, cyclic phosphoesters, and cyclonucleosides. Metathesis [11–14] is a currently useful method in organic chemistry for the synthesis of different nucleoside analogues [15–18]. Len's group developed a concise method for the synthesis of cyclonucleosides via ring-closing metathesis [19, 20]. It was notable that this strategy permits only the synthesis of the 3,5′-*O*-pentanouridine **1** and 3,5′-*O*-hexanouridine **2**. The synthesis of cyclonucleoside having a butyl linker gave only the formation of cyclic dinucleosides **3** and **4** having two butylene between the 5′-O and N-3 position. In this paper, we described a study concerning the synthesis of cyclonucleoside analogues **5** via RCM reaction between the N-3 position and the 5′-C position. Figure 1 gives the structures of **1–5**. We report the *in vitro* anti-HIV evaluation of two compounds.

2 Experimental

2.1 General experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (internal Me_4Si) at 300.13 MHz and at 75.47 MHz, respectively (Bruker Advance-300). TLC was performed on Silica F254 (Merck) and detection was by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was carried out on Silica Gel 60 (Merck, 230 mesh). EtOAc, CH_2Cl_2 and petroleum ether were distilled before use. Bases and solvents were used as supplied. High resolution ESI mass spectra were obtained on a LCT

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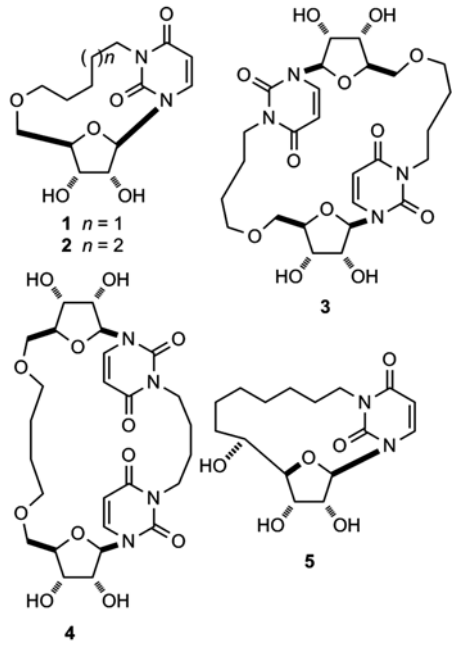


Figure 1 Structures of 3-*N*,5′-*O*-cyclouridines **1** and **2**, cyclic dinucleosides **3** and **4** and 3-*N*,5′-*C*-cyclouridine **5**.

instrument (Micromass-Waters, UK) filled with a lockspray probe. NaI cluster ions were used as the lock mass for accurate mass measurements (resolution FWMH-5000).

2.2 Synthesis of the 2′-*O*-acetyl-3-*N*-allyl-3′,5′-di-*O*-benzyl-5′-*C*-(hex-5-enyl)-uridine

*3-O-Benzyl-1,2-O-isopropylidene-6-O-p-toluenesulfonic-α-D-allofuranose (**8**)*

To a solution of **7** (4.0 g, 12.9 mmol) in CH_2Cl_2 (50 mL) at room temperature was added dibutyltin oxide (64 mg, 0.02 equiv), triéthylamine (1.6 mL, 13 mmol) and *p*-toluenesulfonyl chloride (2.4 g, 13.1 mmol). The reaction mixture was stirred for 24 h and then stopped by adding aq sat $NaHCO_3$ and diluting with CH_2Cl_2. The organic layer was separated, washed with H_2O, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on SiO_2 (EtOAc/petroleum ether, 10/90 *v/v*). Yield: 4.5 g of **8** as colorless oil (75%); R_f 0.6 (hexane-EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H, J = 8.0 Hz, H-Arom), 7.34 (m, 7H, H-Arom), 5.70 (d, J = 3.6 Hz, 1H, H-1), 4.71 and 4.50 (2d, J = 11.4 Hz, 2H, Ph-CH_2), 4.55 (m, 1H, H-2), 4.17–4.06 (m, 3H, H-6, H-5), 3.99 (dd, J = 3.5, 8.7 Hz, 1H, H-4), 3.88 (dd, J = 4.2, 8.7 Hz, 1H, H-3), 2.43 (s, 3H, Ph-CH_3), 1.56 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.9 (C), 137,0 (C), 132.6 (C), 129.9 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 113.3 ($\underline{C}(CH_3)_2$), 104.3 (C-1), 77.4, 77.3, 77.1 (C-2, C-3, C-4), 72.1 (Ph-$\underline{C}H_2$-O), 70.7 (C-6), 69.2 (C-5), 26.8 (CH_3), 26.5 (CH_3), 21.7 (Ph-CH_3). Anal. calcd for $C_{23}H_{28}O_8S$: C, 59.47; H, 6.08; S, 6.90. Found: C, 59.53; H, 6.14; S, 6.87. HRMS (ESI) (M+Na$^+$) calcd for $C_{23}H_{28}O_8SNa$: 487.1403, found 487.1401.

*5,6-Anhydro-O-benzyl-1,2-O-isopropylidene-α-D-allofuranose (**9**)*

To a solution of **8** (7.0 g, 15.1 mmol) in CH_2Cl_2 (10 mL) and MeOH (100 mL), at 0 °C, was added K_2CO_3 (3.1 g, 26.2 mmol). The reaction mixture was stirred at this temperature for 1 h, then for 24 h at room temperature. After dilution with CH_2Cl_2, the mixture was washed with a 1 N aq HCl (20 mL) and then with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on SiO_2 (EtOAc/petroleum ether, 10/90 *v/v*). Yield: 4.0 g of **9** as colorless oil (90%). The physical data were in accordance with those described by Hanaya [21].

*3-O-Benzyl-6-O-deoxy-1,2-O-isopropylidene-6-C-(pent-4-enyl)-α-D-allofuranose (**10**)*

To a solution of **9** (2.0 g, 6.85 mmol) in dry THF (30 mL) in the presence of cuprous iodide (124 mg, 0.69 mmol) was added dropwise at −70 °C a solution of the Grignard reagent (9.2 mL, 13.7 mmol) [freshly prepared in the usual way by controlled addition of 5-bromo-pent-1-ene (2.2 mL, 18.9 mmol) in dry THF (12 mL) to magnesium (1.0 g, 41.6 mmol)]. The solution was stirred for 4 h at −70 °C and then for 12 h at room temperature. The reaction mixture was quenched with aq NH_4Cl (30 mL) and extracted with CH_2Cl_2. The crude product was purified by flash column chromatography on SiO_2 (EtOAc/petroleum ether, 10/90 *v/v*). Yield: 2.2 g of **10** as colorless oil (89%); R_f 0.3 (hexane-EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H, H-arom), 5.80 (ddt, J = 6.7, 10.2, 16.7 Hz, 1H, C$\underline{H}$=CH_2), 5.73 (d, J = 3.9 Hz, 1H, H-1), 5.02–4.90 (m, 2H, CH=C$\underline{H}_2$), 4.75 (d, J = 11.7, 1H, Ph-C$\underline{H}_2$), 4.57 (m, 1H, H-2), 4.56 (d, J = 11.7, 1H, Ph-C$\underline{H}_2$), 4.05 (dd, J = 3.3, 8.7 Hz, 1H, H-4), 3.90 (dd, 1H, J = 4.4, 8.7 Hz, H-4), 3.87 (m, 1H, H-5), 2.04 (m, 2H, CH_2), 1,60 (m, 2H, CH_2), 1.59 (s, 3H, CH_3), 1.39 (m, 4H, 2 CH_2), 1.36 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0 (–CH=), 137.4 (C-arom), 128.4 (CH-arom), 128.1 (CH-arom), 128.0 (CH-arom), 114.3 (CH_2=), 113.0 ($\underline{C}(CH_3)_2$), 104.0 (C-1), 80.7 (C-4), 77.8 (C-2), 77.1 (C-3), 72.1 (Ph-$\underline{C}H_2$-O), 70.8 (C-5), 33.6 (CH_2), 31.8 (CH_2), 28.9 (CH_2), 26.9 (CH_3), 26.6 (CH_3), 25.4 (CH_2). Anal. calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34. Found: C, 69.61; H, 8.40. HRMS (ESI) (M+Na$^+$) calcd for $C_{21}H_{30}O_5Na$: 385.1991, found 385.1987.

*3,5-Di-O-benzyl-6-O-deoxy-1,2-O-isopropylidene-6-C-(pent-4-enyl)-α-D-allofuranose (**11**)*

To a solution of **10** (2.9 g, 8.0 mmol) in THF (30 mL) was added NaH (60% suspension in oil, 800 mg, 20.0 mmol) at room temperature. After 1 h, *tert*-butylammonium iodide (295 mg, 0.8 mmol) and benzyl bromine (2.3 mL, 20 mmol) were added and the mixture was stirred for 12 h at room

temperature. The reaction was quenched by controlled addition of MeOH, poured into sat NH_4Cl and the product extracted with CH_2Cl_2. The extracts were combined, dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on SiO_2 (EtOAc/petroleum ether, 3/97 *v/v*). Yield: 3.0 g of **11** as colorless oil (84%); R_f 0.8 (hexane-EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 10H, H-arom), 5.80 (ddt, J = 6.7, 10.2, 16.7 Hz, 1H, C<u>H</u>=CH_2), 5.68 (d, J = 3.9 Hz, 1H, H-1), 5.02–4.90 (m, 2H, CH=C<u>H</u>$_2$), 4.73 (d, J = 11.7 Hz, 1H, Ph-CH_2), 4.67 (d, J = 11.7 Hz, 1H, Ph-C<u>H</u>$_2$), 4.52 (d, J = 3.9 Hz, 1H, H-2), 4.56 (d, J = 11.7 Hz, 2H, Ph-CH_2), 4.18 (dd, J = 3.3, 8.7 Hz, 1H, H-4), 4.02 (dd, 1H, J = 4.5, 8.7 Hz, H-3), 3.70 (m, 1H, H-5), 2.00 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.59 (s, 3H, CH_3), 1.39 (m, 4H, 2 CH_2), 1.36 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1 (–CH=), 138.9 and 137.7 (C-arom), 128.4 (CH-arom), 128.2 (CH-arom), 128.0 (CH-arom), 127.8 (CH-arom), 127.7 (CH-arom), 127.4 (CH-arom), 114.3 (CH_2=), 112.8 (<u>C</u>$(CH_3)_2$), 103.9 (C-1), 81.5, 78.2, 77.9 and 77.3 (C-2, C-3, C-4, C-5), 73.5 (Ph-<u>C</u>H_2-O), 72.1 (Ph-<u>C</u>H_2-O), 33.6 (CH_2), 30.8 (CH_2), 28.8 (CH_2), 27.0 (CH_3), 26.7 (CH_3), 25.7 (CH_2). Anal. calcd for $C_{28}H_{36}O_5$: C, 74.31; H, 8.02. Found: C, 74.27; H, 8.07. HRMS (ESI) (M+Na^+) calcd for $C_{28}H_{36}O_5Na$: 475.2460, found 475.2457.

*1,2-Di-O-acetyl-3,5-di-O-benzyl-6-O-deoxy-6-C-(pent-4-enyl)-α-D-allofuranoside and 1,2-di-O-acetyl-3,5-di-O-benzyl-6-O-deoxy-6-C-(pent-4-enyl)-β-D-allofuranoside (**12**)*

A solution of **11** (500 mg, 1.1 mmol) in 30 mL of CH_2Cl_2/CF_3COOH/H_2O (5:3:2 *v/v/v*) was stirred for 18 h at room temperature and then quenched by sat $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and the solvent was removed in vacuo. To the residue dissolved in pyridine (3 mL) was added acetic anhydride (0.4 mL, 4.4 mmol). The reaction was stirred at room temperature for 12 h, poured into an iced aq 1 N HCl and extracted with Et_2O. The extracts were combined, dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on SiO_2 (EtOAc/petroleum ether, 5/95 *v/v*). Yield: 1.2 g of a mixture of **12** in a 4:1 ratio (68%); For **12** (α-D) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 10H, H-arom), 6.10 (s, 1H, H-1), 5.72 (ddt, J = 6.7, 10.2, 16.7 Hz, 1H, C<u>H</u>=CH_2), 5.32 (d, J = 4.5 Hz, H-2), 5.02–4.90 (m, 2H, CH=C<u>H</u>$_2$), 4.68 (d, J = 11.7 Hz, 1H, Ph-CH_2), 4.59–4.17 (m, 3H, Ph-CH_2), 4.44 (dd, J = 4.5, 7.6 Hz, 1H, H-3), 4.18 (dd, 1H, J = 2.8, 7.6 Hz, H-4), 3.65 (m, 1H, H-5), 2.10 (m, 3H, CH_3), 1.99 (m, 2H, CH_2), 1.82 (s, 3H, CH_3), 1.47–1.29 (m, 6H, 3 CH_2). For **12** (β-D) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H, H-arom), 6.40 (d, J = 4.5 Hz, 1H, H-1), 5.80 (ddt, J = 6.7, 10.2, 16.7 Hz, 1H, C<u>H</u>=CH_2), 5.09 (dd, J = 4.6, 6.1 Hz, 1H, H-2), 4.96 (m, 2H, CH=C<u>H</u>$_2$), 4.67–4.51 (m, 4H, 2Ph-C<u>H</u>$_2$), 4.30 (t, J = 3.0 Hz, 1H, H-4), 4.23 (dd, 1H, J = 3.0, 6.1 Hz, H-3), 3.55 (m, 1H, H-5), 2.13 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.95–1.20 (m, 8H, 4 CH_2).

*3′-O-acetyl-3′,5′-di-O-benzyl-5′-C-(hex-5-enyl)-uridine (**13**)*

To a solution of uracile (448 mg, 4 mmol) in CH_3CN (8 mL) was added *N,O*-bis(trimethylsilyl)acetamide (BSA) (2 mL, 8 mmol) at room temperature. The reaction was refluxed for 4 h and then cooled at 0 °C. After addition of a solution of **12** (500 mg, 1 mmol) in CH_3CN (8 mL) $SnCl_4$ (0.94 mL) were added. The mixture was stirred at room temperature for 12 h and extracted with CH_2Cl_2. The organic layer was washed with sat NH_4Cl, dried on Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by flash column chromatography on SiO_2 (CH_2Cl_2). Yield: 425 mg of **13** as colorless oil (77%); R_f 0.5 (hexane-EtOAc, 70:30); ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 9,2 (br s, NH), 7.36 (m, 11H, H-arom, H-6), 6.14 (d, J = 5.1 Hz, 1H, H-1′), 5.78 (ddt, J = 5.9, 10.5, 17.3 Hz, 1H, CH_2=C<u>H</u>), 5.18 (t, J = 5.1 Hz, 1H, H-2′), 5.13 (d, J = 8.4 Hz, 1H, H-5), 5.0 (m, 2H, C<u>H</u>$_2$=), 4.77 (d, J = 11.1, 1H, Ph-C<u>H</u>$_2$), 4.59 (d, J = 11.1, 1H, Ph-C<u>H</u>$_2$), 4.49 (d, J = 11.1, 1H, Ph-C<u>H</u>$_2$), 4.38 (d, J = 11.1, 1H, Ph-C<u>H</u>$_2$), 4.33 (t, J = 5.1 Hz, 1H, H-3′), 4.17 (m, 1H, H-4′), 3.72 (m, 1H, H-5′), 2.10 (s, 3H, C<u>H</u>$_3$CO), 2.04 (m, 2H, CH_2) 1.80 (m, 2H, CH_2), 1.50 (m, 4H, 2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (CH_3<u>C</u>O), 163.4 (C-4), 150.7 (C-2), 140.2 (C-6), 138.9 (–CH=), 138.1 and 137.6 (C-arom), 129.1 (CH-arom), 128.9 (CH-arom), 128.7 (CH-arom), 128.4 (CH-arom), 128.5 (CH-arom), 127.9 (CH-arom), 115.1 (CH_2=), 103.0 (C-5), 86.8 (C-1′), 84.7 (C-4′), 79.6 (C-5′), 75.8 and 74.8 (C-2′ and C-3′), 73.5 (Ph-<u>C</u>H_2-O), 72.9 (Ph-<u>C</u>H_2-O), 33.9 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 21.3 (CH_3). Anal. calcd for $C_{31}H_{36}N_2O_7$: C, 67.87; H, 6.61; N, 5.11. Found: C, 67.83; H, 6.65; N, 5.07. HRMS (ESI) (M+Na^+) calcd for $C_{31}H_{36}N_2O_7Na$: 571.2420, found 571.2416.

*3′-O-acetyl-3-N-allyl-3′,5′-di-O-benzyl-5′-C-(hex-5-enyl)-uridine (**14**)*

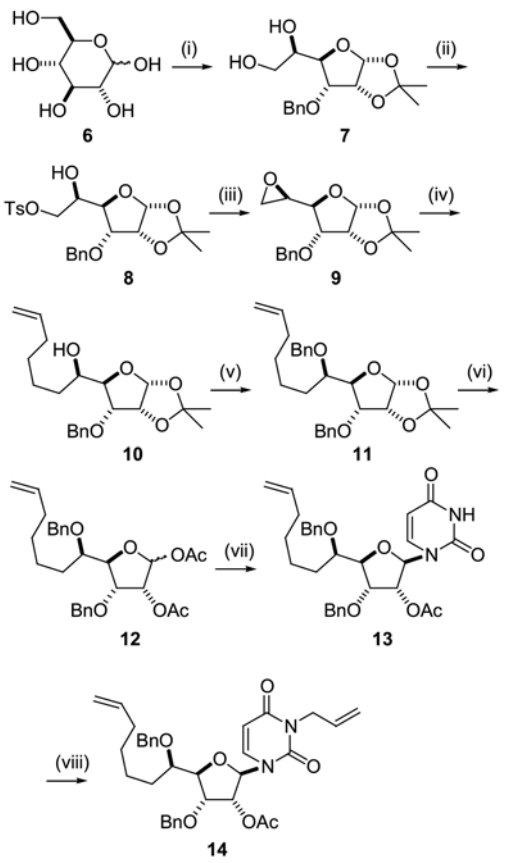
To a solution of **13** (1.2 g, 2.2 mmol) in a mixture of acetone (5 mL) and DMF (5 mL) at room temperature were added K_2CO_3 (395 mg, 2.9 mmol) and allyl bromide (0.2 mL, 2.8 mmol). The mixture was stirred at 60 °C for 12 h, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on SiO_2 (CH_2Cl_2). Yield: 1.1 g of **14** as colorless oil (84%); R_f 0.6 (hexane-EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 11H, H-arom, H-6), 6.13 (d, J = 5.1 Hz, 1H, H-1′), 5.80 (m, 2H, CH_2=C<u>H</u>), 5.22–5.07 (m, 4H, H-2′, H-5, C<u>H</u>$_2$=), 4.95–4.87 (m, 2H, C<u>H</u>$_2$=), 4.76 (d, J = 11.1, 1H, Ph-C<u>H</u>$_2$), 4.59 (d, J = 11.1, 1H, Ph-C<u>H</u>$_2$), 4.40 (m, 3H, Ph-C<u>H</u>$_2$, NC<u>H</u>$_2$), 4.38 (d, J = 11.1, 1H, Ph-C<u>H</u>$_2$), 4.33 (t, J = 5.3 Hz, 1H, H-3′), 4.18 (m, 1H, H-4′), 3.75 (m, 1H, H-5′), 2.10 (s, 3H, CH_3CO), 2.04 (m, 2H, C<u>H</u>$_2$), 1.38-1.80 (m, 6H, 3 CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (CH_3<u>C</u>O), 162.5 (C-4), 151.0 (C-2), 138.9 (C-6), 138.1 (–CH=) 137.6 (C-arom), 131.8 (–CH=), 129.1 (CH-arom), 128.9

(CH-arom), 128.7 (CH-arom), 128.4 (CH-arom), 128.5 (CH-arom), 127.9 (CH-arom), 118.3 (CH_2=), 115.1 (CH_2=), 102.4 (C-5), 87.8 (C-1′), 84.3 (C-4′), 79.4 (C-5′), 75.3 (C-3′), 74.8 (C-2′), 73.5 (Ph-$\underline{C}H_2$-O), 72.9 (Ph-$\underline{C}H_2$-O), 43.5 (CH_2), 33.9 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 21.3 (CH_3). Anal. calcd for $C_{34}H_{40}N_2O_7$: C, 69.37; H, 6.85; N, 4.76. Found: C, 69.36; H, 6.91; N, 4.71. HRMS (ESI) ($M+Na^+$) calcd for $C_{34}H_{40}N_2O_7Na$: 611.2733, found 611.2728.

3 Results and discussion

Toward the synthesis of 3-*N*,5′-*C*-cyclonucleosides

To obtain the desired 3-*N*,5′-*C*-cyclonucleoside **5**, one route has been investigated starting from D-glucose (**6**). The choice to use **6** as starting material conducted us to invert the configuration of the carbon atom in position 3 (hydroxyl group in β position to α position) to have the D-ribose configuration as natural nucleoside. The well-established protection of **6** followed by successive oxidation, selective reduction to obtain the D-allose derivative [22], benzylation of the hydroxyl group in position 3 [23, 24] and deprotection of the diol in position 5,6 [24, 25] gave the D-allose derivative **7** in 51% overall yield (five steps). At this step it was notable that the oxidative cleavage followed by addition of the hex-5-ene magnesium bromide could be studied. In our hand, the reaction was not diastereoselective and a mixture of two diastereoisomers was obtained. Due to this poor selectivity a strategy generating no stereogenic centre via epoxide intermediate was studied. Selective tosylation of the primary hydroxyl group using tosyl chloride in presence of Bu_2SnO and triethylamine furnished compound **8** in 75% yield [26, 27]. Treatment of **8** with K_2CO_3 in methanol gave the epoxide **9** in 90% yield [26, 28] and then the oxirane **9** was reacted in presence of CuI in THF with pent-4-ene magnesium bromide to give selectively the (*R*) alcohol **10** in 89% yield. This condensation has occurred without any loss in the chiral integrity of the (*R*)-configuration at the C5 centre. Treatment of compound **10** with NaH in THF during one hour at room temperature followed by addition of tetrabutylammonium iodide and benzyl bromide gave after one night at room temperature the dibenzylated D-allose derivative **11** in 84% yield. Successive hydrolysis of the acetonide group of compound **11** with acidic treatment using a mixture of dichloromethane-trifluoroacetic acid-water (5:3:2) and then acetylation afforded the diacetate **12** as a mixture of two diastereoisomers α-D and β-D-allose derivatives in a ratio 4:1 in 68% yield. This later mixture **12** was successfully subjected to the corresponding β-nucleoside **13** in 77% yield as the sole product using Vorbruggen condensation reaction [29]. The uracil was silylated using BSA in refluxing CH_3CN and then the mixture of **12** was added followed by the addition of $SnCl_4$ at room temperature [30]. It is clear that the acetate group on C-2′ participated in neighboring group stabilization through the acetyloxonium ion intermediate to favor the formation of the desired β-nucleoside analogue **13**. To prepare selectively the corresponding 3-*N*-allyl derivative **14** reactions of uridine analogue **13** with allyl bromide using a battery of base catalysts were studied. In our hand the best result was obtained using K_2CO_3. Selective *N*-allylation was performed with K_2CO_3 and allyl bromide in DMF and acetone at 55°C to produce the diene **14** in 84% yield (Scheme 1). The diene **14** was subject to the Ring-Closing Metathesis in various solvents and temperatures under first and second generations of Grubbs catalysts, respectively. Also, the Hoveyda- Grubbs catalyst was used under the same conditions but with no ring-closed product formed. A mixture of starting material **14** and dimers was observed as reported by our group for the preparation of 3-*N*,5′-*O*-cyclonucleosides. In our hand,



Scheme 1 Synthesis of 3′-*O*-acetyl-3-*N*-allyl-3′,5′-di-*O*-benzyl-5′-*C*-(hex-5-enyl)-uridine (**14**). Reaction conditions: (i) refs. [21–24]; (ii) 0.02 equiv Bu_2SnO, 1.0 equiv Et_3N, 1.0 equiv TsCl, CH_2Cl_2, 24 h, room temperature; (iii) 1.7 equiv K_2CO_3, CH_2Cl_2, MeOH, 0 °C for 1 h and then room temperature for 24 h; (iv) 0.1 equiv CuI, 2.7 equiv CH_2=CHC_3H_6MgBr, THF, –70°C for 4 h and then room temperature for 12 h; (v) 2.5 equiv NaH, THF, room temperature for 1 h and then 0.1 equiv Bu_4NI, 2.5 equiv BnBr, room temperature for 12 h; (vi) CH_2Cl_2, CF_3COOH, H_2O, room temperature for 18 h and then Ac_2O, pyridine, room temperature for 12 h; (vii) 4 equiv uracile, 8 equiv BSA, CH_3CN, reflux for 4 h and then $SnCl_4$, room temperature, 12 h; (viii) 1.3 equiv K_2CO_3, 1.3 equiv CH_2=$CHCH_2Br$, acetone, DMF, 60 °C, 12 h.

no 3-*N*,5′-*C*-cyclonucleoside was obtained using the developed strategy.

4 Conclusions

In summary, this strategy using Ring-Closing Metathesis did not permit the synthesis of the cyclonucleoside having a heptyl linker between the 5′-C and 3-N positions. One possibility will be the enhancement of the number of carbon atoms. These potential structures having octyl or nonyl linker could be prepared using Ring-Closing Metathesis but will not have the properties of a restricted nucleoside analogue. In anti-HIV studies, compounds **13** and **14** were evaluated for their inhibitory effects on the replication of HIV-1 in human T4-lymphoblastoid cells, CEM-SS and MT-4. Compounds **13** and **14** have been found inactive against HIV-replication at concentrations up to 10 μM.

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