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An efficient synthesis of dienic nucleoside analogues via a Mitsunobu reaction

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Abstract—Nucleoside analogues **9** and **12** were obtained in good yields from alcohol **7** which, under Mitsunobu conditions, led to the title products after deprotection steps.

1. Introduction

Among nucleoside analogues synthesized in recent years, some of them displayed a significant antiviral activity. In the search for new compounds, the major modifications were carried out on the sugar moiety of the nucleoside.[1–4] The interest in the synthesis of acyclic nucleoside compounds emerged when it appeared that changing the ribose moiety by an acyclic chain leads to potent anti-viral drugs,[2] such as ganciclovir **1** (Fig. 1),[3] which shows anti-herpetic activity. The acyclic chain may be indeed considered as resulting from the suppression of a methylene group with respect to a carbohydrate moiety.[5] This means that the total structure of the glycosyl portion is then not necessarily required for the biological activity.[6] In the course of our research program towards carbocyclic nucleoside analogues,[7] we took into account the fact that the replacement of the oxygen atom by a methylene group increases the stability of the analogue against phosphorylases and hydrolases. An example in the field of acyclic compounds is penciclovir **2**.[7] It is the reason why we wish to report here the synthesis of carba-acyclic nucleoside analogues.

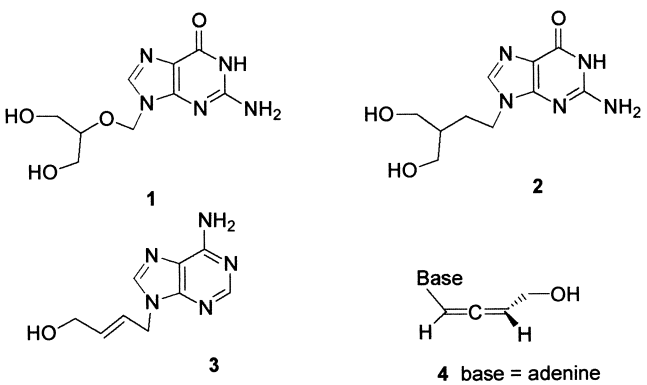

Figure 1.

The structure modifications, which were proposed, tended to modify the flexibility of the chain between the base and the hydroxymethylene group. This chain flexibility allowed the non-natural substrate to improve the interactions with the enzyme, with respect to the natural one.[8] For instance, Hua et al.[6] synthesized a neplanocin A analogue **3**. The introduction of a double bond gave a slight rigidity to the analogue, which might stabilize the compound in the best conformation to improve the interactions between the phosphorylating enzymes and the analogue. In the case of thymallene[9] or adenallene **4**,[10] the rigidity induced by the cumulated double bond system is counteracted by the free rotation of the base and the hydroxymethylene function. In our concern, we planned to prepare analogues with a dienic structure (Fig. 2), which could present a compromise between a flexible saturated chain and a more rigid one as in adenallene **4**.

Figure 2.

2. Results and discussion

The previously obtained dienic alcohol **5**[11] (Scheme 1) was protected as a *tertio*butyldiphenylsilyl ether to give compound **6**. First attempts of reduction of the ester

Keywords: cyclobutenes; dienes; Mitsunobu reactions; nucleoside analogues.

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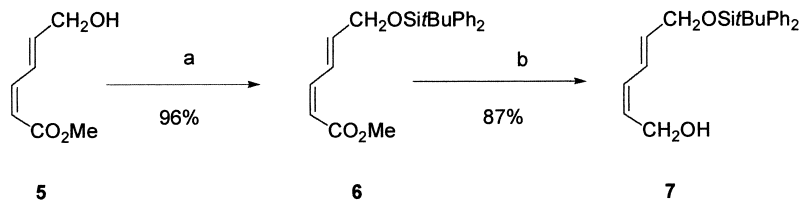
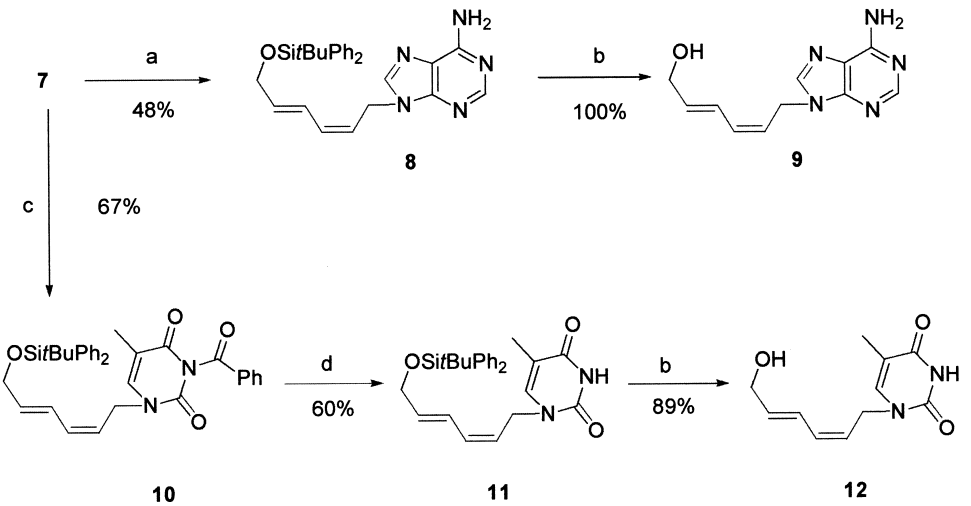


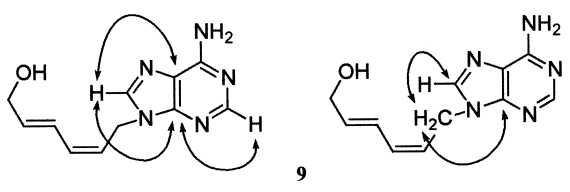
Scheme 1. *Conditions* (a) *t*BuPh$_2$SiCl/imidazole/DMF, 14 h; (g) DIBALH/toluene, −60°C, 1 h.



Scheme 2. *Conditions* (a) PPh$_3$/DEAD/adenine/THF (b) *n*-TBAF/THF (c) PPh$_3$/DEAD/*N*-3-benzoylthymine/THF (d) NH$_4$OH/MeOH.

function by aluminium hydride[12,13] gave no result, but alcohol **7** was obtained by reduction of the conjugated ester **6** with diisobutylaluminium hydride[14]. The alcohol **7** was treated with adenine, triphenylphosphine and DEAD under Mitsunobu conditions (Scheme 2). The expected compound **8** was obtained in reasonable yield (48%). It should be noticed that only the N-9 regioisomer is formed and not another substitution product (Scheme 3). The cleavage of the silyl group by tetra-*n*-butylammonium fluoride provided the adenine dienic analogue **9**. The alcohol **7** reacted with *N*-3-benzoylthymine under Mitsunobu conditions to give compound **10** in 67% yield. This compound was successively deprotected with NH$_4$OH/MeOH and tetra-*n*-butylammonium fluoride to obtain the target thymine dienic analogue **12**.

To conclude, in the course of the synthesis of the two new adenine and thymine dienic analogues **9** and **12**, the access to the key intermediate, the alcohol **7**, was allowed by the use of stereo and chemoselective reactions and by appropriate protective steps. The Mitsunobu reaction provided the expected analogues in an efficient way, leading only to the N-9 adenine analogue. Finally, the two new adenine and thymine dienic analogues **9** and **12** were prepared,



9

Scheme 3. Relevant ^{1}H/^{13}C HMBC correlations for identification of compound **9** as the N-9 regioisomer.

respectively, in seven steps (21% overall yield from the cyclobutene anhydride precursor of **5**) and in eight steps (16% overall yield from the same anhydride). These compounds were evaluated for their anti-HIV activity but no significant activity was detected.

3. Experimental

3.1. General

NMR spectra were recorded at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. IR spectra were recorded with a FT infrared spectrophotometer. Melting points are uncorrected. Elemental analyses were performed by the service of microanalyses, CNRS ICSN, Gif sur Yvette. The column chromatography were run on silica gel Gerudan SI 60, 230–400 mesh, under 1–2 bar.

3.1.1. Methyl (2*Z*,4*E*)-6-([*tert*-butyl(diphenyl)silyl]oxy)-hexa-2,4-dienoate 6. To a sample of alcohol **5**[11] (343 mg, 0.85 mmol) in DMF (520 μL) were added *tert*-butyldiphenylsilyl chloride (684 μL) and imidazole (181 mg). The mixture was stirred 14 h at room temperature and water (1.2 mL) was added. After extraction with ether (4×1.4 mL), the combined organic extracts were dried (MgSO$_4$), the solvent was removed under reduced pressure and the residue was purified by column chromatography (cyclohexane/ethyl acetate 95/5) to give **6** (884 mg, 96%) as an oil. ^{1}H NMR (δ_{ppm}) ($CDCl_3$): 7.71–7.55 (5H; m); 7.45–7.34 (6H; m); 6.59 (1H; dd; J=11.3, 11.6 Hz); 6.09 (1H; dt; J=4.4, 15.2 Hz); 5.65 (1H; d; J=11.3 Hz); 4.34 (2H; dd; J=1.7, 4.4 Hz); 3.72 (3H; s); 1.09 (9H; s). ^{13}C NMR (δ_{ppm})

($CDCl_3$): 166.7; 143.9; 142.2; 135.5; 133.3; 129.7; 127.7; 125.6; 117.0; 63.8; 51.1; 26.8; 19.2. IR (ν cm^{-1}) (film): 1720; 1644; 1602. Anal. calcd for $C_{23}H_{28}SiO_3$ ($+0.2H_2O$): C 71.91; H 7.40. Found: C 71.84; H 7.36.

3.1.2. (2*Z*,4*E*)-6-([*tert*-Butyl(diphenyl)silyl]oxy)hexa-2,4-dien-1-ol 7. To a solution of ester **6** (884 mg, 2.3 mmol) in toluene (125 mL) at −60°C was added a 1 M solution of DIBALH in toluene (11.6 mL, 11.6 mmol). After 1 h at −60°C the mixture was hydrolyzed with 10% citric acid (98 mL). The aqueous layer was extracted with toluene (2×30 mL) and the combined organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (cyclohexane/ethyl acetate 95/5) to give **7** (717 mg, 87%) as an oil. ^{1}H NMR (δ_{ppm}) ($CDCl_3$): 7.71–7.64 (4H; m); 7.45–7.35 (6H; m); 6.58 (1H; ddtd; *J*=1.2, 1.7, 11.3, 15.1 Hz); 6.11 (1H; ddt; *J*=5.5, 11.1, 11.3 Hz); 5.82 (1H; dt; *J*=4.7, 15.1 Hz); 5.59 (1H; dtd; *J*=1.2, 6.6, 11.1 Hz); 4.30 (2H; dd; *J*=5.5, 6.6 Hz); 4.27 (2H; dd; *J*=1.7, 4.7 Hz); 1.6 (1H; s broad); 1.07 (9H; s).^{13}C NMR (δ_{ppm}) ($CDCl_3$): 135.5; 134.4; 133.5; 130.1; 129.7; 129.0; 127.7; 124.0; 63.9; 58.8; 26.9; 19.2. IR (ν cm^{-1}) (film): 3365; 1469; 1110; 1049. Anal. calcd for $C_{22}H_{28}SiO_2$: C 74.19; H 7.92. Found: C 74.18; H 7.73.

3.1.3. 9-[(2*Z*,4*E*)-6-([*tert*-Butyl(diphenyl)silyl]oxy)hexa-2,4-dienyl]-9*H*-purin-6-amine 8. To a solution of alcohol **7** (612 mg, 1.73 mmol), triphenylphosphine (989 mg) and adenine (495 mg) in THF (10 mL), was added, dropwise over a period of 2.5 h, a solution of DEAD (552 μL) in THF (10 mL). The mixture was stirred for 48 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate/methanol 9/1) to give **8** (398 mg, 48%) as a white powder. Mp: 137.0–138.3°C (ether/methanol 9/1). ^{1}H NMR (δ_{ppm}) ($CDCl_3$): 8.37 (1H; s); 7.77 (1H; s); 7.73–7.65 (4H; m); 7.48–7.35 (6H; m); 6.75 (1H; ddtd; *J*=0.6, 1.8, 4.8, 11.5 Hz); 6.33 (1H; ddt; *J*=5.5, 11.1, 11.5 Hz); 5.95 (1H; dt; *J*=4.3, 14.8 Hz); 5.94 (2H; s); 5.59 (1H; dtd; *J*=0.6, 7.3, 11.1 Hz); 4.91 (2H; dd; *J*=5.5, 7.4 Hz); 4.33 (2H; dd; *J*=1.8, 4.3 Hz); 1.08 (9H; s). ^{13}C NMR (δ_{ppm}) ($CDCl_3$): 156.0; 153.4; 149.5; 140.2; 137.1; 135.9; 133.7; 133.4; 130.2; 128.1; 123.1; 122.7; 119.8; 64.2; 40.8; 27.2; 19.6. IR (ν cm^{-1}) (KBr disk): 3305; 3126; 1668; 1594; 1301; 1110; 1049. Anal. calcd for $C_{27}H_{31}SiN_5O$: C 69.05; H 6.65; N 14.91. Found: C 69.21; H 6.55; N 14.77.

3.1.4. 9-[(2*Z*,4*E*)-6-Hydroxyhexa-2,4-dienyl]-9*H*-purin-6-amine 9. To a solution of protected alcohol **8** (124 mg, 0.26 mmol) in THF was added *n*-tetrabutylammonium fluoride (1 M, 532 μL) and the mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (dichloromethane/methanol 5/1) to give **9** (61 mg, 100%) as a white powder. Mp: 197.7–198.6°C (methanol). ^{1}H NMR (δ_{ppm}) (DMSO-D6): 8.14 (1H; s); 8.11 (1H; s); 7.21 (2H; s); 6.72 (1H; ddtd; *J*=0.6, 1.8, 11.3, 15.0 Hz); 6.20 (1H; ddt; *J*=5.5, 10.6, 11.3 Hz); 5.93 (1H; dt; *J*=5.2, 15.0 Hz); 5.56 (1H; dtd; *J*=0.6, 7.1, 10.6 Hz); 4.92 (2H; dd; *J*=5.5, 7.1 Hz); 4.89 (1H; t; *J*=5.4 Hz); 4.06 (2H; ddd; *J*=1.8, 5.2, 5.4 Hz). ^{13}C NMR (δ_{ppm}) (DMSO-D6): 155.8; 152.4; 149.2; 140.3; 137.5; 131.4; 124.0; 123.3; 118.5; 61.1; 40.0. IR (ν cm^{-1}) (KBr disk): 3401; 3363/3268; 1679; 1600; 1332. Anal. calcd for $C_{11}H_{13}N_5O$: C 57.13; H 5.66; N 30.28. Found: C 56.97; H 5.77; N 30.51.

3.1.5. 1-[(2*Z*,4*E*)-6-([*tert*-Butyl(diphenyl)silyl]oxy)hexa-2,4-dienyl]-3-benzoyl-5-methylpyrimidine-(1*H*,3*H*)-dione 10. To a solution of alcohol **7** (1.200 g, 3.4 mmol), triphenylphosphine (1.803 g) and *N*-3-benzoylthymine (1.561 g; 6.8 mmol) in THF (21 mL), was added, dropwise over a period of 2.5 h, a solution of DEAD (1 mL) in THF (21 mL). The mixture was stirred for 48 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (cyclohexane/ethyl acetate 4/1) to give **10** (1.293 g, 67%) as a white powder. Mp: 53.6–55.4°C. ^{1}H NMR (δ_{ppm}) ($CDCl_3$): 7.93 (2H; dd; *J*=1.2, 8.4 Hz); 7.69–7.63 (5H; m); 7.62 (2H; t; *J*=1.5 Hz); 7.52–7.35 (6H; m); 6.99 (1H; q; *J*=1.2 Hz); 6.66 (1H; ddtd; *J*=0.6, 1.2, 11.3, 14.8 Hz); 6.33 (1H; ddt; *J*=5.5, 10.6, 11.3 Hz); 5.96 (1H; dt; *J*=4.3, 15.0 Hz); 5.43 (1H; dtd; *J*=0.6, 7.5, 10.6 Hz); 4.49 (2H; dd; *J*=5.5, 7.5 Hz); 4.32 (2H; dd; *J*=1.2, 4.3 Hz); 1.93 (3H; d; *J*=1.2 Hz). ^{13}C NMR (δ_{ppm}) ($CDCl_3$): 168.1; 162.6; 149.5; 139.0; 136.9; 135.4; 134.9; 133.5; 133.3; 131.6; 130.4; 129.7; 129.0; 127.7; 122.5; 122.2; 110.9; 63.8; 44.4; 26.8; 19.2; 12.4. IR (ν cm^{-1}) (KBr disk): 1747; 1697; 1646; 1434; 1228; 1110. Anal. calcd for $C_{34}H_{36}SiN_2O_4$: C 70.07; H 6.57; N 4.81. Found: C 70.08; H 6.32; N 4.75.

3.1.6. 1-[(2*Z*,4*E*)-6-([*tert*-Butyl(diphenyl)silyl]oxy)hexa-2,4-dienyl]-5-methylpyrimidine-(1*H*,3*H*)-dione 11. To a solution of **10** (257 mg, 0.45 mmol) in methanol (11.5 mL) was added a solution of 20.5% ammonium hydroxide in water (4.5 mL). The mixture was stirred for 48 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (cyclohexane/ethyl acetate 3/1) to give **11** (126 mg, 60%) as a white powder. Mp: 146.3–146.8°C (petroleum ether/ether 2/1). ^{1}H NMR (δ_{ppm}) ($CDCl_3$): 8.37 (1H; s); 7.71–7.65 (4H; m); 7.47–7.36 (6H; m); 6.90 (1H; q; *J*=1.2 Hz); 6.66 (1H; ddtd; *J*=0.6, 1.2, 11.1, 14.8 Hz); 6.30 (1H; ddt; *J*=5.5, 10.6, 11.3 Hz); 5.94 (1H; dt; *J*=4.3, 14.8 Hz); 5.40 (1H; dtd; *J*=0.6, 7.4, 10.6 Hz); 4.44 (2H; dd; *J*=5.5, 7.4 Hz); 4.33 (2H; dd; *J*=1.2, 4.3 Hz); 1.89 (3H; d; *J*=1.2 Hz); 1.09 (9H; s). ^{13}C NMR (δ_{ppm}) ($CDCl_3$): 164.2; 151.0; 139.4; 136.6; 135.5; 133.4; 133.2; 129.8; 127.7; 122.8; 122.7; 63.8; 44.2; 26.8; 19.3; 12.4. IR (ν cm^{-1}) (KBr disk): 3438; 3153; 1671; 1652; 1425; 1355; 1218; 1105; 1029. Anal. calcd for $C_{27}H_{32}SiN_2O_3$: C 70.40; H 7.00; N 6.08. Found: C 70.65; H 7.01; N 5.91.

3.1.7. 1-[(2*Z*,4*E*)-6-Hydroxyhexa-2,4-dienyl]-5-methylpyrimidine-(1*H*,3*H*)-dione 12. To a solution of **11** (124 mg, 0.27 mmol) in THF (2.4 mL) was added tetra-*n*-butylammonium fluoride (1 M, 539 μL). The mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (dichloromethane/methanol 9/1) to give **12** (54 mg, 89%) as a white powder. Mp: 140.1–140.7°C. ^{1}H NMR (δ_{ppm}) (CD_3OD): 7.36 (1H; q; *J*=1.1 Hz); 6.71 (1H; ddtd; *J*=0.6, 1.5, 11.3, 15.0 Hz); 6.26 (1H; ddt; *J*=5.6, 10.8, 11.3 Hz); 5.94 (1H; dt; *J*=5.4, 15.0 Hz); 5.43 (1H; dtd; *J*=0.6, 7.1, 10.8 Hz); 4.50 (2H; dd; *J*=5.6, 7.1 Hz); 4.18 (2H; dd; *J*=1.5, 5.4 Hz); 1.85 (3H; d;

J=1.1 Hz). ^{13}C NMR (δ_{ppm}) (CD_3OD): 166.8; 152.8; 142.3; 137.4; 133.5; 125.4; 124.8; 111.4; 63.1; 45.7; 12.2. IR (ν cm^{-1}) (KBr disk): 3500; 3147; 1695; 1671; 1473; 1355; 1218; 1085. Anal. calcd for $C_{11}H_{14}N_2O_3$: C 59.45; H 6.35; N 12.60. Found: C 59.41; H 6.18; N 12.44.

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