Pergamon

Tetrahedron 58 (2002) 3775–3778

TETRAHEDRON

A short route to new cyclobutene nucleoside analogues

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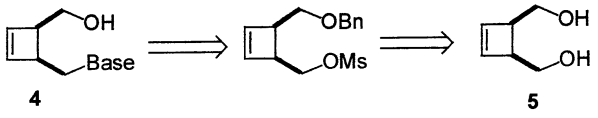
Received 28 November 2001; revised 11 March 2002; accepted 18 March 2002

Abstract—Nucleoside analogues (+)-**4a** and (+)-**4b** were obtained in non-racemic form by a short and efficient way. The key step was a Mitsunobu reaction of alcohol (−)-**8** with adenine or protected thymine. The title products were obtained after deprotection steps.

1. Introduction

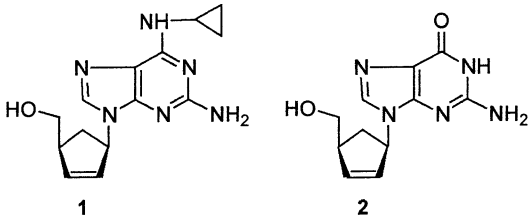
Unsaturated nucleoside analogues are an interesting class of biologically active compounds and several of them show a significant antiviral activity. Among the new structures synthesized during the past decade, those containing a carbocycle are particularly promising.[1] The advantage of these analogues, in which the sugar moiety was replaced by a carbocycle, is their better stability toward the phosphorylase enzymes, which cleave the glycosidic linkage. Many structures were proposed including cyclopropane,[2,3] cyclobutane,[4] cyclopentane,[5] cyclohexane,[6] bicyclic[7] and even an acyclic chain.[8] Among these, (−)-abacavir **1**,[9a] and (−)-carbovir **2**,[9b] were reported to be potent inhibitors of the HIV-1 reverse transcriptase. Previous works in our laboratory led to the synthesis of nor-carbovir **3a**[10a] and of the analogue **3b**.[10b] These two molecules do not show any activity against HIV-1. The lack of activity may be due to the shorter distance than in normal nucleosides between the 5′-OH moiety and the base. To check this point we synthesized cyclobutenic derivatives **4** including a methylene spacer between the carbocycle and the heterocycle. We thereby restored the four atom link between both of them as in carbovir **2** (Fig. 1).

We first investigated some synthetic ways in the racemic series (Scheme 1). They started from diol **5** prepared by reduction of 3-oxabicyclo[3.2.0]hept-6-en-2,4-dione[11] with lithium aluminum hydride (LAH). In the first route, the monobenzylated derivative[12] was converted into mesylate. The subsequent substitution with the adenine/K_2CO_3/18-crown-6 mixture in DMF for 44 h at 30°C or with the thymine/K_2CO_3/18-crown-6 mixture in DMSO at 30°C for 44 h led to the expected products in low yield. Moreover they were formed together with other regioisomers and separations were difficult. The predominant isomers gave the target molecules by deprotection with BCl_3. An



4 **5**

Scheme 1.



1 **2**

3a Base = 9-guanyl (+)-**4a** Base = 9-adenyl
3b Base = 9-adenyl (+)-**4b** Base = thymine

Figure 1.

Keywords: cyclobutenes; asymmetric synthesis; Mitsunobu reactions; nucleoside analogues.

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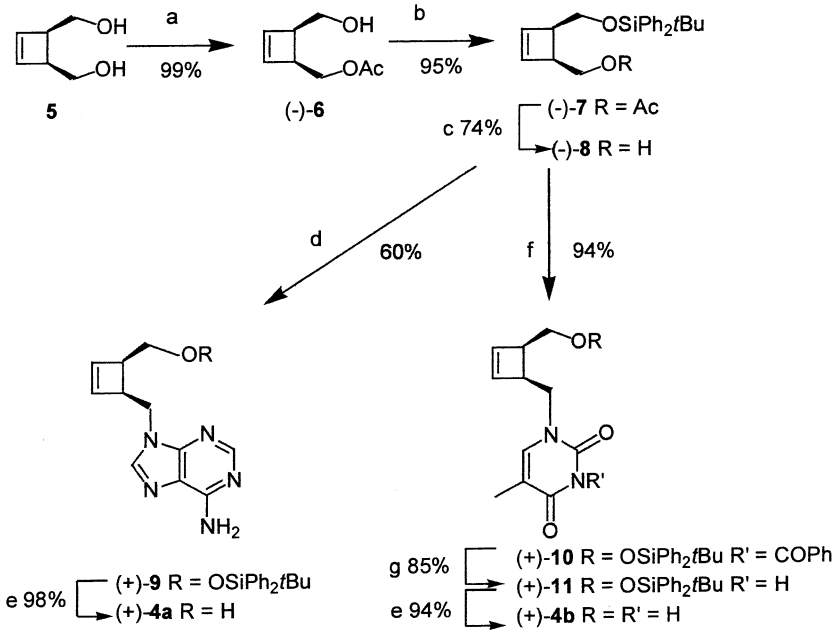

Scheme 2. *Conditions*: (a) PFL/vinyl acetate −18°C 19 h; (b) *t*BuPh$_2$SiCl/imidazole/DMF; (c) NH$_3$/MeOH (d) PPh$_3$/DEAD/adenine/THF; (e) TBAF/THF; (f) PPh$_3$/DEAD/*N*-3-benzoylthymine; (g) NaOH.

alternative way to avoid obtaining of the unwanted regioisomers was to build the heterocyclic moiety from an amino group. Therefore the preceding mesylate was converted to an azide which was reduced with LAH. Known procedures[13,14] led to the expected purine and pyrimidine derivatives in poor overall yield (18 and 15%, respectively, from amine).

In carbovir only the minus enantiomer is biologically active. Therefore we tried to synthesize these molecules in enantiomerically enriched form and with the same configurations (1*S*,4*R*) as in carbovir or abacavir. The key intermediate was one of the two cyclobutenic mono-acetates derived from alcohol **5** (Scheme 2). The starting material for a non-racemic route was alcohol (−)-**6** obtained by a recently reported method.[15] Unfortunately this alcohol could not be benzylated and classical conditions led to a mixture of the corresponding diacetate and dibenzylate. Alternative methods in acidic media,[16,17] led to decomposition of the starting material. Finally we could obtain alcohol (−)-**8** by protection of the alcohol (−)-**6** as a silyl derivative followed by treatment with NH$_3$/MeOH to remove the acetyl group. A first attempt of introducing adenine base directly under Mitsunobu conditions (Scheme 2) and in standard conditions gave the desired product but in low yield (Table 1). Fortunately replacement of dioxane by THF as solvent led to an improvement of the yield of (+)-**9** up to 60% (entry 4).

Table 1.

Entry	Reagents	Solvent	Time	Yield (%)
1	PPh$_3$/DEAD	Dioxane	14 h	24
2	PPh$_3$/DEAD	Dioxane	5 Days	37
3	PPh$_3$/DIAD	Dioxane	14 h	34
4	PPh$_3$/DEAD	THF	7 Days	60
5	PPh$_3$/DEAD	Benzene	5 Days	38

This method is interesting because it needs only one step. Moreover, in these conditions, only the more stable N-9 isomer was obtained probably due to a thermodynamic control. Deprotection with tetrabutylammonium fluoride led to the nucleoside analogue (+)-**4a** in good yield. Similarly alcohol (−)-**8** reacted with the protected thymine to give cyclobutene (+)-**10**, in very good yield (94%). This compound was deprotected by treatment with NaOH/dioxane then tetrabutylammonium fluoride to obtain (+)-**4b**.

To conclude, we have synthesized the two non-racemic nucleoside analogues (+)-**4a** and (+)-**4b**, respectively, in six steps (33% overall yield from the starting anhydride) and in seven steps (42% overall yield from the starting anhydride). Mitsunobu reaction proved to be efficient to introduce purine or pyrimidine bases directly from a primary alcohol. (+)-**4a** and (+)-**4b** were tested against HIV-1 but none of them had a significant antiviral activity.

2. Experimental

2.1. 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. High-resolution mass measurements were performed at the CRMPO (Rennes). The column chromatographies were run on silica gel Gerudan SI 60, 230–400 mesh, under 1–2 bar.

2.1.1. (−)-[(1*S*,4*R*)-4-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)cyclobut-2-enyl]methyl acetate (−)-7. To a sample of alcohol **6**[15] (91.8% ee,1.4 g, 8.97 mmol) in

DMF (2.1 mL) were added *tert*-butyldiphenylsilyl chloride (2.8 mL) and imidazole (737 mg). The mixture was stirred overnight at room temperature and water (5 mL) was added. After extraction with ether (4×11 mL), the combined organic extracts were dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue purified by column chromatography (cyclohexane/ethyl acetate 95/5) to give (−)-**7** (3.35 g, 95%) as an oil. $[\alpha]_D^{20°C}=-4.7$ (c=1.51 $CHCl_3$). ^1H NMR (δ_{ppm}) ($CDCl_3$): 7.69–7.63 (4H; m); 7.44–7.34 (6H; m); 6.19 (1H; d; J=2.5 Hz); 6.09 (1H; d; J=2.5 Hz); 4.35 (1H; dd; J=6.7; 11.0 Hz); 4.21 (1H; dd; J=7.3; 11.0 Hz); 3.85 (2H; d; J=6.8 Hz); 3.27–3.11 (2H; m); 1.98 (3H; s); 1.04 (9H; s). ^{13}C NMR (δ_{ppm}): 171.0; 138.6; 137.9; 135.7; 133.7; 129.7; 127.8; 64.8; 63.9; 47.8; 44.4; 27.0; 20.9; 19.2. Anal. calcd for $C_{24}H_{30}SiO_3$: C 73.05; H 7.66. Found: C 72.97; H 7.82.

2.1.2. (−)-[(1*S*,4*R*)-4-({*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-cyclobut-2-enyl]methanol (−)-8. To a solution of acetate **7** (3.35 g, 8.5 mmol) in methanol (80 mL) at 0°C, was added a saturated solution of ammonia in methanol (161 mL). The mixture was stirred for 48 h at room temperature. After removal of the volatile substances, the residue was purified by column chromatography (cyclohexane/ethyl acetate 7/1) to give (−)-**8** (2.2 g, 74%). $[\alpha]_D^{20°C}=-6.5$ (c=1.32 $CHCl_3$). ^1H NMR (δ_{ppm}) ($CDCl_3$): 7.67 (4H; dd; J=7.8; 1.5 Hz); 7.47–7.35 (6H; m); 6.01 (1H; d; J=2.8 Hz); 5.84 (1H; d; J=2.8 Hz); 3.81–3.75 (5H; m); 3.31 (1H; ddd; J=3.8; 7.8; 9.2 Hz); 3.15 (1H; ddd; J=3.8; 5.4; 6.6 Hz); 1.04 (9H; s). ^{13}C NMR (δ_{ppm}): 138.0; 136.6; 135.6; 132.7; 129.9; 127.9; 63.9; 62.2; 48.8; 47.7; 26.9; 19.1. Anal calcd for $C_{22}H_{28}SiO_2$ C 74.99; H 8.00. Found: C 74.78; H 8.12.

2.1.3. (+)-9-[(1*S*,4*R*)-4-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)cyclobut-2-enyl]methyl-9*H*-purin-6-ylamine (+)-9. To a solution of alcohol **8** (609 mg, 1.73 mmol), triphenylphosphine (987 mg) and adenine (493 mg) in THF (10 mL), was added dropwise for 2.5 h a solution of DEAD (550 μL) in THF (10 mL). The mixture was stirred for one week 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 (+)-**9** (487 mg, 60%) as white needles. Mp: 134.4–135.2°C (ether/petroleum ether 3/1). $[\alpha]_D^{20°C}=+0.94$ (c=1.27 $CHCl_3$). ^1H NMR (δ_{ppm}) ($CDCl_3$): 8.38 (1H; s); 7.80 (1H; s); 7.67 (4H; m); 7.47–7.37 (6H; m); 6.14 (2H; s); 6.09 (1H; d; J=2.9 Hz); 6.08 (1H; d; J=2.9 Hz); 4.63 (1H; dd; J=5.9; 13.8 Hz); 4.32 (1H; dd; J=10.3; 13.8 Hz); 3.90 (1H; dd; J=5.4; 11.0 Hz); 3.85 (1H; dd; J=7.9; 11.0 Hz); 3.51 (1H; m); 3.24 (1H; m); 1.10 (9H; s). ^{13}C NMR (δ_{ppm}): 155.5; 152.9; 150.1; 140.5; 138.6; 138.7; 135.6; 135.5; 133.4; 133.3; 129.8; 129.7; 127.7; 119.7; 63.4; 47.5; 45.4; 44.5; 26.9; 19.2. Anal. calcd for $C_{27}H_{31}SiN_5O$: C 69.05; H 6.65; N 14.91. Found: C 68.98; H 6.66; N 14.68.

2.1.4. (+)-{(1*S*,4*R*)-4-[(6-Amino-9*H*-purin-9-yl)methyl]-cyclobut-2-enyl}methanol (+)-4a. Tetrabutylammonium fluoride (602 μL of 1 M in THF) was added to a solution of **9** (140 mg, 0.30 mmol) in THF (2.7 mL). After stirring for 2 h, the volatile substances were removed under reduced pressure and the residue purified by column chromatography (dichloromethane/methanol 5/1) to give (+)-**4a** (68 mg, 98%). $[\alpha]_D^{20°C}=+34.4$ (c=1.08 DMSO). Mp: 126.4–127.4°C (methanol). ^1H NMR (δ_{ppm}) (DMSO-d_6): 8.15 (1H; s); 8.12 (1H; s); 7.17 (2H; broad s); 6.19 (1H; d; J=2.7 Hz); 6.08 (1H; J=2.7 Hz); 4.69 (1H; t; J=4.9 Hz); 4.42 (1H; dd; J=6.0; 13.7 Hz); 4.20 (1H; dd; J=9.8; 13.7 Hz); 3.67–3.51 (2H; m); 3.49–3.40 (1H; m); 3.05 (1H; m). ^{13}C NMR (δ_{ppm}) (DMSO-d_6): 155.9; 152.3; 149.5; 140.8; 138.8; 138.5; 118.7; 60.6; 47.6; 44.8; 43.3. IR (ν cm^{-1}) (KBr disc): 3390; 3293; 3118; 1673; 1602. Anal. calcd for $C_{11}H_{13}N_5O$: C 57.13; H 5.66; N 30.28. Found: C 57.57; H 5.84; N 30.34.

2.1.5. (+)-1-{[(1*S*,4*R*)-4-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)cyclobut-2-enyl]methyl}-3-benzoyl-5-methyl-pyrimidine-(1*H*,3*H*)-dione (+)-10. To a solution of alcohol **8** (662 mg, 1.90 mmol), triphenylphosphine (996 mg) and *N*-3-benzoylthymine[18] (861 mg) in THF (12 mL), was added dropwise for 2.5 h a solution of DEAD (585 μL) in THF (12 mL). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate/methanol 4/1) to give *N*-benzoyl (+)-**10** (998 mg, 94%) as white needles. Mp: 116.2–116.8°C (ether/petroleum ether 2/1). $[\alpha]_D^{20°C}=+20.8$ (c=1.27 $CHCl_3$). ^1H NMR (δ_{ppm}) ($CDCl_3$): 7.93 (2H; dd; J=0.9; 8.1 Hz); 7.68–7.63 (5H; m); 7.62 (2H; dd; J=1.2; 1.2 Hz); 7.52–7.35 (6H; m); 7.07 (1H; dd; J=1.1 Hz); 6.16 (1H; d; J=2.4 Hz); 6.05 (1H; d; J=2.4 Hz); 4.23 (1H; dd; J=4.8; 13.6 Hz); 3.85 (1H; dd; J=10.3; 13.6 Hz); 3.86 (1H; dd; J=4.8; 11.1 Hz); 3.77 (1H; dd; J=7.6; 11.1 Hz); 3.33 (1H; ddd; J=4.3; 4.8; 10.3 Hz); 3.20 (1H; ddd; J=4.3; 4.8; 7.6 Hz); 1.92 (3H; d; J=1.1 Hz); 1.07 (9H; s). ^{13}C NMR (δ_{ppm}): 168.5; 162.6; 149.2; 140.8; 138.5; 138.3; 135.8; 135.1; 133.5; 131.9; 130.7; 130.1; 129.3; 128.0; 110.8; 63.8; 50.2; 47.2; 44.9; 27.2; 19.5; 12.7. Anal. calcd for $C_{34}H_{36}SiN_2O_4$ (+0.25 H_2O): C 71.74; H 6.37; N 4.92. Found C 71.75; H 6.37; N 4.79.

2.1.6. (+)-*N*-1-{[(1*S*,4*R*)-4-({[*tert*-Butyl(diphenyl)silyl]-oxy}methyl)cyclobut-2-enyl]methyl}-5-methyl-pyrimidine-(1*H*,3*H*)-dione (+)-11. To a solution of **10** (104 mg, 0.18 mmol) in dioxane (1.5 mL), was added NaOH 8N (1.5 mL) and the resulting mixture was stirred for 3 days at room temperature. A 10% solution of hydrochloric acid was added at 5°C to neutralize the base. After extraction with ethyl acetate (10×4 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate 3/1) to give (+)-**11** (72 mg, 85%) as a white powder. Mp: 89.3–92.3°C (petroleum ether/ether 2/1). $[\alpha]_D^{20°C}=+25.1$ (c=1.10 $CHCl_3$). ^1H NMR (δ_{ppm}) ($CDCl_3$): 9.42 (1H; s); 7.71–7.65 (4H; m); 7.48–7.36 (6H; m); 6.97 (1H; d; J=1.2 Hz); 6.14 (1H; d; J=2.8 Hz); 6.05 (1H; d; J=2.8 Hz); 4.20 (1H; dd; J=4.8; 13.5 Hz); 3.86 (1H; dd; J=5.0; 11.0 Hz); 3.8 (1H; dd; J=10.5; 13.5 Hz); 3.78 (1H; dd; J=7.9; 11.0 Hz); 3.31 (2H; ddd; J=4.8; 10.5; 4.5 Hz); 3.19 (2H; ddd; J=4.5; 5.0; 7.9 Hz); 1.89 (3H; d; J=1.2 Hz); 1.08 (9H; s). ^{13}C NMR (δ_{ppm}): 164.8; 151.3; 141.1; 138.6; 138.5; 135.9; 133.8; 130.2; 128.1; 110.8; 63.8; 49.9; 47.9; 44.9; 27.3; 19.6; 12.7. Anal. calcd for $C_{27}H_{32}SiN_2O_3$ (+0.15 H_2O): C 69.99; H 6.96; N 6.04. Found: C 69.92; H 6.99; N 5.86.

2.1.7. (+)-*N*-1-{[(1*S*,4*R*)-4-(hydroxymethyl)cyclobut-2-enyl]methyl}-5-methyl-pyrimidine-(1*H*,3*H*)-dione 4b. To a solution of protected alcohol **11** (222 mg, 0.46 mmol) in THF (4.2 mL), was added tetrabutylammonium fluoride (1 M, 920 μL) and the mixture was stirred for 2 h at room temperature. The solvent was removed in vacuum and the residue was purified by column chromatography (dichloromethane/methanol 9/1) to give (+)-**4b** (96 mg, 94%). $[\alpha]_D^{20°C}$=+61.9 (*c*=1.01 methanol). Mp: 132.8–133.9°C (ether /methanol 6/1). ^{1}H NMR (δ_{ppm}) ($CDCl_3$): 7.45 (1H; q; *J*=1.2 Hz); 6.18–6.15 (2H; m); 4.07 (1H; dd; *J*=5.7; 13.8 Hz); 3.81 (1H; dd; *J*=10.1; 13.8 Hz); 3.74 (1H; dd; *J*=5.9; 11.0 Hz); 3.7 (1H; dd; *J*=8.4; 11.0 Hz); 3.33–3.24 (1H; m); 3.20–3.12 (1H; m); 1.87 (3H; d; *J*=1.2 Hz). ^{13}C NMR (δ_{ppm}) (CD_3OD): 166.8 153.0; 143.3; 139.7; 139.1; 111.0; 62.6; 49.8; 48.8; 45.9; 12.2. IR (ν cm^{-1}) (KBr disc): 3463, 3160, 3027, 1691. Anal. calcd for $C_{11}H_{14}N_2O_3$: C 59.45; H 6.35; N 12.60. Found: C 59.38; H 6.26; N 12.67.

Acknowledgements

We thank the local section of Sarthe of the Ligue Nationale contre le Cancer for a fellowship to C. H.

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