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Malika Nechab [a], Claude Chavis [a], Marc Lucas [a] & Jean-Louis Imbach [a]
[a] Universite de Montpellier II, Sciences et Techniques du Languedoc, Laboratoire de Chimie Bio-Organique , Associe au CNRS n°488, Case 008, 34095, Montpellier Cedex 5, France
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CONVENIENT SYNTHESIS OF (±)1', 2'-*SECO*-2', 3'-METHANONUCLEOSIDES

Malika Nechab, Claude Chavis, Marc Lucas and Jean-Louis Imbach*

Université de Montpellier II, Sciences et Techniques du Languedoc, Laboratoire de Chimie Bio-Organique, Associé au CNRS n°488, Case 008, 34095 Montpellier Cédex 5, France

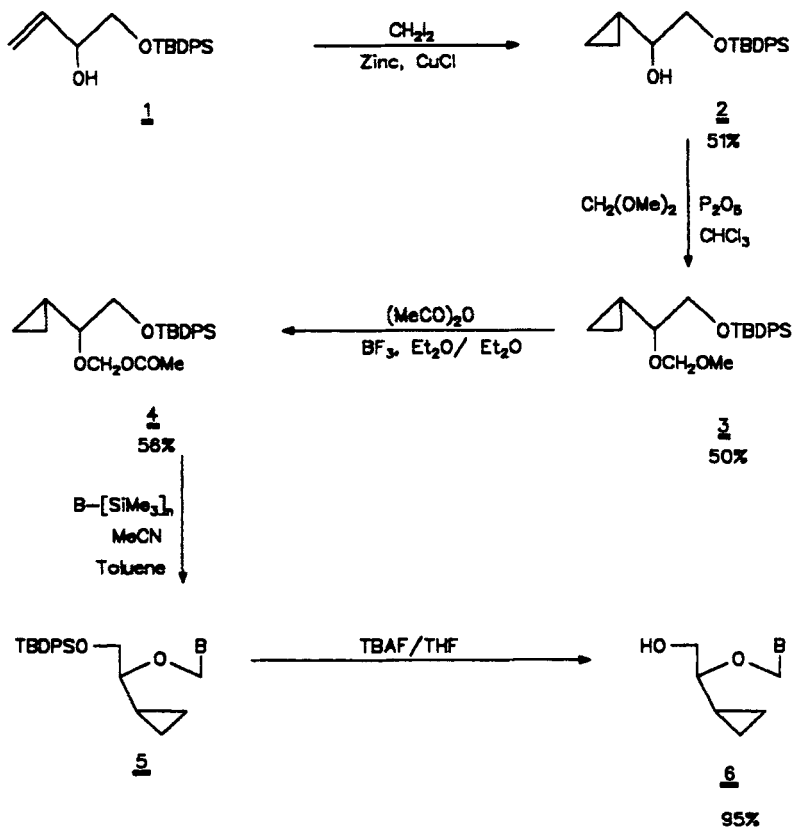
ABSTRACT: *The racemic 1',2'-seco-2',3'-methanonucleosides have been synthesized by a five step chemical sequence. In this way (±)-1-[(1'-hydroxy-3',4'-methylene-but-2'-oxy)methyl]cytosine* **6c**, *thymine* **6a**, *and uracil* **6e** *and (±)-9-[(1'-hydroxy-3',4'-methylene-but-2'oxy)methyl]adenine* **6d** *and guanine* **6b** *have been obtained and their antiviral evaluation is reported.*

Up to now some acyclic modifications in the sugar moiety of nucleosides provided sometimes compounds with very potent antiviral activity *i.e.* acyclovir[1] or DHPG[2].

In continuation of our work on acyclonucleosides[3,4] we prepared a series of compounds bearing a cyclopropano ring on the acyclic side chain of the nucleobase. The rationale behind these acyclic derivatives comes from a constraint imposed on side-chain flexibility by incorporation of a cyclopropane moiety which could result in a better conformation for enzyme interaction[5].

* To whom all correspondence should be addressed.

scheme 1



B	Yield %
5a Th	90
5b Gu	61
5c Cy	78
5d Ad	86
5e Ur	84

* tert–ButylDiPhenylSilyl = TBDPS

One of the prerequisite conditions for such an interaction implies that the nucleosides should be metabolized to their active phosphorylated intermediates.

In addition, the reactive cyclopropane moiety could also play an hypothetic role, under opening conditions, in forming covalent linkages with proteins.

Since the reaction of carbenes is known[6] to produce a methylene bridge across the 5,6 positions of pyrimidine nucleosides, therefore the strategy of our synthesis is described in scheme 1.

The synthetic plan required a coupling step between the appropriate cyclopropanated synthon and the desired silylated nucleobase according to our efficient glycosylation procedure.[4]

The desired nucleosides were synthesized *via* a five step sequence starting with the known[4] derivative **1** which was cyclopropanated in **2** (51%) by means of diodomethane, powdered zinc and cuprous chloride.[7]
Treatment of **2** with dimethoxymethane and phosphorus pentaoxide in chloroform[8] produced **3** (50%) which was acetoxylated (56%) with acetic anhydride and boron trifluoride-diethyl ether at 4°C.

The synthon **4** was used for the coupling step with the five trimethylsilylated nucleobases (scheme 1); this reaction required a solid-liquid phase transfert catalysis with KI-dibenzo 18-crown-6 in toluene and acetonitrile (1:1, v/v). As reported in scheme 1, N-9 purinyl and N-1 pyrimidyl acyclic nucleosides **5a**-**5e** were exclusively obtained in good to excellent yields. The regioisomerism of these compounds was ascertained by UV spectroscopy in two different media.[9] Removal of the TBDPS group with TBAF in THF afforded the unprotected acyclic nucleoside **6a**-**6e** in nearly quantitative yields (95%).

None of the five nucleosides had any effect against various DNA or RNA viruses in cell cultures.

EXPERIMENTAL

M.p.s were obtained with a Büchi (capillary) apparatus and were uncorrected. UV spectra were determined on a Cary 1186 spectrophotometer. Elemental analyses were performed by the 'Service de Microanalyse du CNRS, Division de Vernaison'. ^{1}H NMR spectra were determined on a Brüker AC250, or a Brüker AM300 spectrometer. *J* Values are given in Hz. Mass spectra were obtained with a Jeol JMS-DX300 by the FAB ionization method.

(±)-1-tert-Butyldiphenylsilyloxy-3,4-methylenylbutan-2-ol 2. A mixture of diodomethane (17 cm^3, 0.12 mol), Zn (28.5 g, 0.43 mol) and cuprous chloride (4.13 g, 41.7 mmol) was heated at 80°C and stirred under an atmosphere of argon for 2 h. The reaction mixture was cooled at room temperature and stirred for 1 h more. Then 1 (15 g, 44 mmol) in anhydrous glyme (27 cm^3) was added dropwise under stirring at room temperature for 1 h and then at 60°C for 2 h. After filtration on Celite the solvent was removed under reduced pressure. The crude reaction mixture was flash chromatographed on a silica gel column with petroleum ether-dichloromethane 65:35 as the eluting system and afforded 2 (8 g, 51% yield) as an oil. R_f 0.42 (dichloromethane-petroleum ether 6:4), δ_H(300 MHz, $CDCl_3$) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 1.1 (9H, s, 3Me), 2.65 (1H, m, OH), 3.05 (1H, m, CHOH), 3.75 (2H, m, CH_2OSi),

7.4-7.7 (10H, m, aromatic) (Found: C,73.76; H,8.25 $C_{21}H_{28}O_2Si$. requires C,74.07; H,8.29%).

(±)-1-tert-Butyldiphenylsilyloxy-2-methoxymethylenoxy-3,4-methylenylbutane 3. To a solution of 2 (3.8 g, 11.2 mmol) in anhydrous chloroform (20 cm^3) and formaldehyde dimethylacetal (2.25 cm^3) was added phosphorus pentaoxide (2.28 g) portionwise with vigorous stirring. After 1 h at room temperature the mixture was hydrolyzed by ice-water and neutralized with saturated aqueous $NaHCO_3$. The organic layer was diluted with CH_2Cl_2 and washed with water, decanted and dried (Na_2SO_4) and evaporated under reduced pressure . Column chromatography of the residual oil on silica gel eluted with cyclohexane-diethyl ether 26:4 afforded pure *title compound* 3 (2.10 g, 50% yield) as an oil. R_f 0.63 (cyclohexane-diethyl ether 9:1), δ_H(250 MHz; $CDCl_3$) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 1.1 (9H, s, 3Me), 3.05 (1H, m, CHOH), 3.4 (3H, s, OMe), 3.8 (2H, m, CH_2O), 4.8 (2H, m, OCH_2O), 7.4-7.7 (10H, m, aromatic) (Found: C, 71.68; H, 8.25. $C_{23}H_{32}O_3Si$ requires C, 71.83; H, 8.39%).

(±)-1-tert-Butylphenylsilyloxy-2-acetoxymethylenoxy-3,4-methylenylbutane 4. To a solution of 3 (1.45 g, 3.8 mmol) in anhydrous diethyl ether (18 cm^3) and anhydrous acetic anhydride (0.5 cm^3) at -20°C was added boron trifluoride-diethyl ether (0.14 cm^3). This mixture was stirred at 4°C for 22 h after which it was poured on ice-water, neutralized with saturated aqueous $NaHCO_3$ and extracted twice with diethyl ether. The etheral extracts

were washed once with 10% aqueous $NaHCO_3$, twice with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residual oil was flash chromatographed on a silica gel column with 27:3 cyclohexane-diethyl ether as the eluting system and afforded **4** (0.61 g, 56%). R_f 0.31 (diethyl ether-cyclohexane 5:95), δ_H(250 MHz; $CDCl_3$) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 1.1 (9H, s, 3Me), 2.05 (3H, s, COMe), 3.1 (1H, m, CHO), 3.75 (2H,m, CH_2OSi), 5.4 (2H, m, OCH_2O), 7.4-7.7 (10H, m, aromatic) (Found: C, 69.93; H, 7.90.$C_{24}H_{32}O_4Si$ requires C, 69.86; H, 7.82%).

Preparation of *seco*-nucleosides 5 a-e. General procedure. *Silylation of nucleobases*: unprotected nucleobase (Ad, Cy, Gu, Th, Ur) (6 mmol) in hexamethyldisilazane (25 cm^3) and a catalytic amount of ammonium sulfate were refluxed for 1 d in the case of pyrimidines and for 2 d in the case of purines. The reagent was cautiously removed under reduced pressure.

PTC glycosylation: a solution of **4** (1 mmol) and of silylated nucleobase (1.2 mmol) in acetonitrile-toluene (1/1 v/v; 10 cm^3) containing dibenzo-18-crown-6 ether (0.2 mmol) and potassium iodide (0.8 mmol) was stirred for 2-8 h at 80°C under an atmosphere of argon. The insoluble material was filtered off and the filtrate evaporated under reduced pressure to give an oil which was chromatographed on silica gel, using methanol-dichloromethane as the eluting system.

(±)-1-[(1'-tert-Butyldiphenylsilyloxy-3',4'-methylenylbut-2'-oxy)methyl]thymine 5a. The *title compound* was obtained as an oil following the

aforementioned procedure (2 h). After chromatography with methanol-dichloromethane (3:97) as the eluent **5a** was obtained as an oil (90.5% yield). R_f 0.68 (methanol-dichloromethane 5:95), λ_{max}(EtOH, 95%)/nm 265, δ_H(300 MHz; $CDCl_3$) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 1.1 (9H, s, 3Me), 1.85 (3H, s, Me), 3 (1H, m, CHO), 3.75 (2H, m, CH_2OSi), 5.3 (2H, m, OCH_2N), 7.15 (1H, d, *J* 1.2 , 6-H), 7.4-7.7 (10H, m, aromatic) (Found: C, 67.78; H, 7.28; N, 6.05. $C_{27}H_{34}N_2O_4Si$ requires C, 67.75; H, 7.16; N, 5.85%).

(±)-9-[(1'-tert-Butyldiphenylsilyloxy-3',4'-methylenylbut-2'-oxy)methyl]guanine 5b. The *title compound* was obtained as an oil following the aforementioned procedure (3 h). After chromatography with methanol-dichloromethane (6:94) as the eluent **5b** was recrystallized (61% yield) from methanol-dichloromethane, m.p. 210°C decomp, R_f 0.73 (dichloromethane-methanol 85:15), λ_{max}(EtOH, 95%)/nm 250, δ_H(300 MHz; [$^2H_6$] DMSO) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (m, 1H, cyclopropyl), 1.1 (9H, s, 3Me), 3.1-3.2 (1H, m, CHO), 3.6 (2H, m, CH_2OSi), 5.4-5.7 (2H, m, OCH_2N), 6.2-6.4 (2H, s, NH_2), 7.4-7.7 (10H, m, aromatic), 7.75-8.05 (1H, s, 8-H), 10.64 (1H, m, NH) (Found: C, 59.26; H, 6.85. $C_{27}H_{33}N_5O_3Si$, 2.5 H_2O requires C, 59.06; H, 6.97%).

(±)-1-[(1'-tert-Butyldiphenylsilyloxy-3',4'-methylenylbut-2'-oxy)methyl]cytosine 5c. The *title compound* was obtained as an oil following the aforementioned procedure (4 h). After chromatography with methanol-dichloromethane (7:93) as the eluent **5c** was obtained as a foam (78% yield). R_f

0.38 (dichloromethane-methanol 9:1), λ_{max}(EtOH, 95%)/nm 270, δ_H(300 MHz; $CDCl_3$) 0.1 (1H, m, cyclopropyl); 0.4 (2H, m, cyclopropyl); 0.55 (1H, m, cyclopropyl); 0.85 (1H, m, cyclopropyl); 1.1 (9H, s, 3Me), 1.75 (2H, m, NH_2), 3.0 (1H, m, CHO), 3.75 (2H, m, CH_2OSi), 5.3 (2H, m, OCH_2N), 5.6 (1H, d, *J* 7.28 , 5-H), 7.4-7.7 (10H, m, aromatic) (Found: C, 66.67; H, 7.1; N, 8.84. $C_{26}H_{33}N_3O_3Si$, 0.25 H_2O requires C, 66.70; H, 7.21; N, 8.92%).

(±)-9-[(1'-tert-Butyldiphenylsilyloxy-3',4'-methylenylbut-2'-oxy)methyl]adenine 5d. The *title compound* was obtained as an oil following the aforementioned procedure (4 h). After chromatography with methanol-dichloromethane (2:98) as the eluent **5d** was obtained as a yellow oil (86% yield). R_f 0.54 (dichloromethane-methanol 9:1), λ_{max}(EtOH, 95%)/nm 258, δ_H(300 MHz; $CDCl_3$), 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 1.1 (9H, s, 3Me), 3.05 (1H, m, CHO), 3.75 (2H, m, CH_2OSi), 5.75 (2H, m, CH_2N), 5.95 (2H, s, NH_2), 7.4-7.7 (10H, s, aromatic) (Found: C, 66.4; H, 6.83; N, 13.75. $C_{27}H_{33}N_5O_2Si$ requires C, 66.5; H, 6.82; N, 14.36%).

(±)-1-[(1'-tert-Butyldiphenylsilyloxy-3',4'-methylenylbut-2'-oxy)methyl]uracil 5e. The *title compound* was obtained as an oil following the aforementioned procedure (3 h). After chromatography with methanol-dichloromethane (3:97) as the eluent **5e** was obtaind as a yellow foam (84% yield). R_f 0.78 (dichloromethane-methanol 85:15), λ_{max}(EtOH, 95%)/nm 258; δ_H(300 MHz; $CDCl_3$), 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 1.1 (9H, s, 3Me), 3

(1H, m, CHO), 3.75 (2H, m, CH_2OSi), 5.3 (2H, m, OCH_2N), 5.65 (1H, d, *J* 7.94 , 5-H), 7.4-7.7 (10H, m, aromatic) (Found: C, 65.01; H, 6.92; N, 5.67. $C_{26}H_{32}N_2O_4Si$, 1 MeOH requires C, 65.29; H, 7.31; N, 5.64%).

Desilylation of *seco*-nucleosides. General procedure.

To a stirred solution of silylated acyclonucleoside **5** (1 mmole) in THF (2.5 cm^3) was added a solution (3 mmol, 0.9 cm^3) of tetrabutylammonium fluoride (1.1 mol/dm^3 in THF) at room temperature for 3h. The solvent was evaporated under reduced pressure and the free seconucleoside **6** was obtained in 95% yield after chromatography or recrystallization.

(±)-1-[(1'-Hydroxy-3',4'-methylenylbut-2'-oxy)methyl]thymine 6a. R_f 0.58 (dichloromethane-methanol 85:15), m.p. 105-107°C (from CH_2Cl_2), λ_{max}(EtOH, 95%)/nm 263, λ_{max}(0.1 mol/dm^3 KOH)/nm 265, δ_H(300 MHz; [$^2H_6$] DMSO) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 1.75 (3H, s, Me), 2.95 (1H, m, CHO), 5.1 (2H, m, OCH_2N), 7.55 (1H, s, 6-H), 11.2 (1H, d, NH) (Found: C, 54.88; H, 6.69; N, 11.52. $C_{11}H_{16}N_2O_4$ requires C, 54.99; H, 6.71; N, 11.66%).

(±)-9-[(1'-Hydroxy-3',4'-methylenylbut-2'-oxy)methyl]guanine 6b. M.p. >250°C (from methanol), R_f 0.37 (dichloromethane-methanol 85:15), λ_{max}(EtOH, 95%)/nm 251, λ_{max}(0.1 mol/dm^3 KOH)/nm 266, δ_H(300 MHz; [$^2H_6$] DMSO) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 3.0 (1H, m, CHO), 3.4

(2H, m, CH_2OH), 4.65 (1H, m, OH), 5.4-5.6 (1H, q, *J* 10.3, OCH_2N), 6.2-6.5 (2H, s, NH_2), 7.75-8.05 (1H, s, 8-H), 10.65 (1H, m, NH). FAB-MS (thioglycerol) m/e 266 $[M+H]^+$, 152 $[BH+H]^+$.

(±)-1-[(1'-hydroxy-3',4'-methylenylbut-2'-oxy)methyl]cytosine 6c. R_f 0.33 (dichloromethane-methanol 85:15), λ_{max}(EtOH, 95%)/nm 268, λ_{max}(0.1 mol/dm^3 HCl)/nm 277, δ_H(300 MHz; [$^2H_6$] DMSO) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 2.95 (1H, m, CHO), 3.4 (2H, m, CH_2OH), 4.65 (1H, t, *J* 5.72, OH), 5.15 (2H, s, OCH_2N), 5.7 (1H, d, *J* 7.25, 5-H), 7.15 (2H, d, *J* 42.19, NH_2), 7.6 (1H, d, *J* 7.27 , 6-H). FAB-MS (thioglycerol) m/e 226 $[M+H]^+$, 112 $[BH+H]^+$.

(±)-9-[(1'-Hydroxy-3',4'-methylenylbut-2'-oxy)methyl]adenine 6d. R_f 0.46 (dichloromethane-methanol 85:18), m.p. 201-203°C (from CH_2Cl_2), λ_{max}(EtOH, 95%)/nm 258, λ_{max}(0.1 mol/dm^3 KOH)/nm 259, δ_H(300 MHz; [$^2H_6$] DMSO) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl), 3.05 (1H, m, CHO), 3.4 (2H, m, CH_2OH), 4.75 (1H, t, *J* 5.34 , OH), 5.64 (2H, m, OCH_2N), 7.25 (2H, s, NH_2), 8.15 (1H, s, 2-H), 8.25 (1H, s, 8-H) (Found: C, 52.25; H, 6.07; N, 27.13. $C_{11}H_{15}N_5O_2$, 0.25 H_2O requires C, 52.06; H, 6.16; N, 27.60%).

(±)-1-[(1'-Hydroxy-3',4'-methylenylbut-2'-oxy)methyl]uracil 6e. R_f 0.43 (dichloromethane-methanol 85:15), m.p. 120-122°C (from CH_2Cl_2-

MeOH), λ_{max}(EtOH, 95%)/nm 258, λ_{max}(0.1 mol/dm³ HCl)/nm 259, δ_H(300 MHz; [$^2H_6$] DMSO) 0.1 (1H, m, cyclopropyl), 0.4 (2H, m, cyclopropyl), 0.55 (1H, m, cyclopropyl), 0.85 (1H, m, cyclopropyl),2.95 (1H, m, CHO), 3.4 (2H, m, CH_2N), 4.65 (1H, t, *J* 5.6, OH), 5.15 (2H, m, OCH_2N), 5.6 (1H, d, *J* 7.82, 5-H), 7.6 (1H, d, *J* 8.04, 6-H), 11.25 (1H, s, NH) (Found: C, 49.71; H, 5.9; N, 11.03. $C_{10}H_{14}N_2O_4$, 0.25 CH_2Cl_2 requires C, 49.75; H, 5.91; N, 11.32%).

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