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Synthesis of Unsaturated Silicon Analogues of Acyclonucleosides

Laurent Latxague, Jacques Thibon and Gérard Déléris*

Laboratoire de Chimie Bio-Organique, Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, F-33076 Bordeaux Cedex, France

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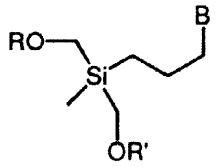
Abstract: Unsaturated acyclic sila-thymidine analogues were prepared in order to improve their rigidity and to seek better pairing with complementary nucleotides.

Modified nucleoside analogues incorporable in oligodeoxynucleotide (ODN) solid-phase synthesis for use as oligonucleotide-based or antisense prodrugs [1] might improve cellular penetration and nuclease resistance. To avoid the stereochemical complexity of the sugar moiety, we designed and previously synthesized [2, 3] acyclic nucleoside analogues which contain: (a) a silicon atom in place of the carbon-4' of the deoxyribose in order to improve the overall lipophilicity, (b) two hydroxymethyl groups to anchor the target within the ODN, and (c) a propyl chain linking the silicon to a nucleic base.



B= T, A, C, G

R= R'= OH then
R= DMTr and R'= (O)P(NiPr$_2$)CH$_2$CH$_2$CN

The three-carbon chain length was chosen to avoid β-elimination of the nucleobase which might occur with a two-carbon chain, even though this shorter spacer mimics more closely the actual nucleoside structure. However, a preliminary study of the stability of a ACTTGCTTTTGACACAA duplex containing up to 3 modified thymidine or adenosine analogues [4] revealed a destabilization of base pairing as the melting temperatures were lowered by 7.5 to 12°C for each analogue incorporated into a strand. In fact, this destabilization is comparable to that observed with pure carbon acyclonucleoside analogues [5]. This result, along with molecular modeling observations, encouraged us to undertake the synthesis of more strained molecules.

Therefore, the present work describes the synthesis of *unsaturated* acyclic thymidine analogues with a Z/E 2-propenyl and vinylidene ethyl structure.

Thus, Z isomers **1a** and **1b** were prepared according to Scheme 1. Propargyl thymine **7**, obtained in 80% yield from propargyl bromide and in situ-generated bis(trimethylsilyl)thymine, was converted into a magnesium acetylide and then reacted at low temperature with both chloromethyldimethylchlorosilane or bis(chloromethyl)methylchlorosilane to give **6a** (60%) and **6b** (19%).

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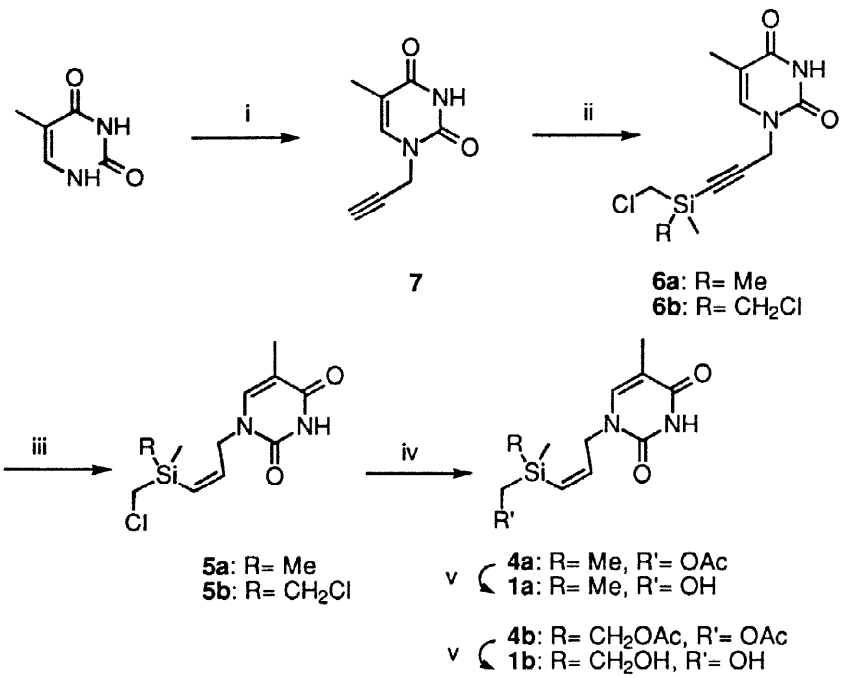
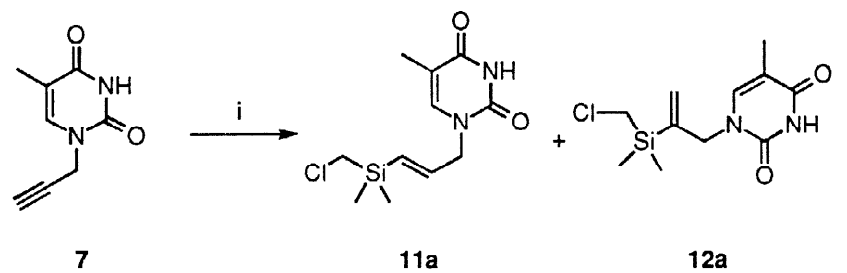


Sheme 1 - i: 1) HMDS, Me_3SiCl 2) propargyl bromide, DMF 3) H_2O ii: 1) EtMgBr 2) $ClCH_2Si(Me)(R)H$, -30°C 3) H_2O iii: H_2, $Pd/BaCO_3$, quinoline iv: AcONa, DMF v: APTS, MeOH.

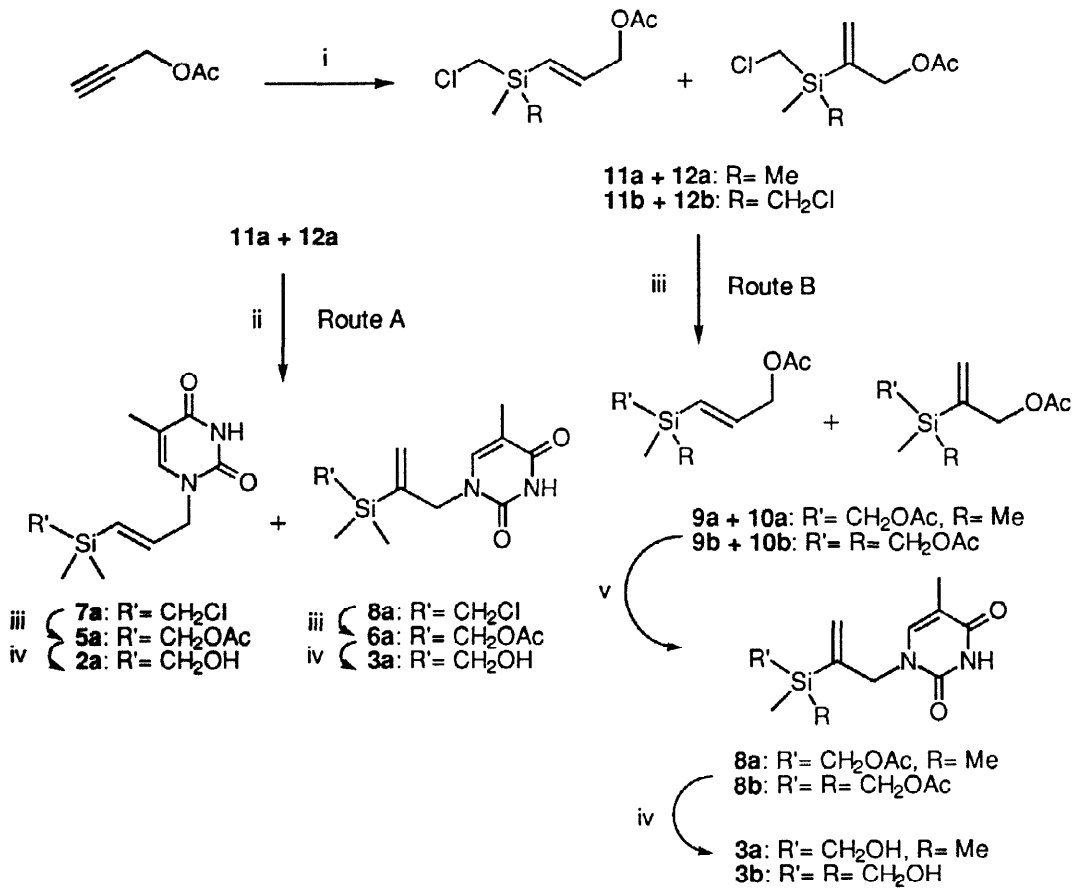
Hydrogenation over palladium-on-barium carbonate as catalyst in the presence of quinoline to prevent further reduction yielded **5a** (74%) and **5b** (70%). Nucleophilic displacement of chlorine in the latter compounds by the acetate ion gave esters **4a** (30%) and **4b** (39%), which were treated with MeOH/H$^+$ to yield **1a** [6] (80%) and **1b**[7] (52%) respectively.

To prepare the E isomers, propargyl thymine **7**, which was first protected by means of HMDS/Me_3SiCl, was subjected to a hydrosilylation reaction with chloroplatinic acid as catalyst to give the trans 2-propenyl **11a** and vinylidene ethyl **12a** isomers (Scheme 2). Unfortunately, both were obtained insufficiently at this early stage of the synthesis (6 and 11% repectively).



Scheme 2 - i: $ClCH_2Si(Me)(Me)H$, H_2PtCl_6, THF.

Previous reports of a successful palladium-catalysed addition of the sodium salt of nucleoside bases [8] or nucleoside base analogues to allylic acetate [9] by way of a Trost reaction [10], prompted us to investigate this method. This was performed on a propargyl acetate silylated adduct (Scheme 3).



Scheme 3 - i: $ClCH_2Si(Me)(R)H$, H_2PtCl_6, THF ii: Sodium salt of thymine/DMF, $Pd_2(dba)_3$/dppe/THF iii: AcONa, DMF iv: MeOH, PTSA v: Sodium salt of thymine/DMF, $Pd(PPh_3)_4$/THF.

Thus, in the presence of chloroplatinic acid, commercial propargyl acetate reacted with chloromethyldimethylsilane or bis(chloromethyl)methylchlorosilane to give a 1:1 mixture of **11a/12a** in a 70% yield, and **11b/12b** in a 88% yield. The two isomers could not be easily separated so the mixture was used thereafter. Compounds **11a/12a** were reacted with the sodium salt of thymine (route A) in the presence of tris(benzylideneacetone)palladium(0) and 1,2-bis(diphenylphosphino)ethane (dppe) to give **7a** (14%) and **8a** (28%), which could both be separated on a silica gel column. The two compounds were treated with the acetate ion to give **5a** (43%) and **6a** (50%), and then **2a** [11] (72%) and **3a**[12] (70%) upon treatment with MeOH/H$^+$. When applied to the **11b/12b** mixture (step ii, route A), this scheme gave very poor yields and numerous by-products. Thus, the synthetic route B was used as an alternative. Prior to the Trost reaction conducted with tetrakis(triphenylphosphine)palladium(0), compounds **11a/12a** and **11b/12b** were treated with the acetate ion to give **9a/10a** (95%) and **9b/10b** (77%). Surprisingly, the **9a,b/10a,b** mixtures gave **8a** (10%) and **8b** (15%) only when subjected to the Trost reaction, whereas **9a,b** were recovered in unreacted form. Finally, compounds **8a** and **8b** reacted in MeOH/H$^+$ afforded the mono- and dihydroxylated compounds **3a** and **3b** [13] respectively in 83 and 53% yield.

Thus, a new access to novel unsaturated nucleoside analogues has been found. These derivatives might be of some interest as antimetabolites, so we are presently testing their ability to be phosphorylated by cellular kinases. Moreover, after tritylation and activation as 2-cyanoethyl *N,N*-diisopropylphosphoramidite, they will

be incorporated into oligonucleotides, where we expect an improvement of their hybridization properties with the complementary strand.

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4. Unpublished results Dr. S. Moreau, INSERM ; bold letters give the position of the various substitutions: TGAACGAAACTGTGTT, TGAACGAAACTGTGTT AND TGAACGAAACTGTGTT.
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6. Satisfactory spectroscopic data (200 MHz ^{1}H, 50 MHz ^{13}C and MS) were obtained for all new compounds. **1a**, ^{1}H NMR ($CDCl_3$) 0.18 (s, 6H, CH_3Si), 1.84 (s, 3H, CH_3 thymine), 2.43 (s, 1H, OH), 3.49 (s, 2H, $C\underline{H}_2OH$), 4.40-4.43 (d, 2H, J = 6.2 Hz, CH_2N), 5.76-5.83 (d, 1H, J = 14 Hz, CHSi), 6.17-6.31 (m, 1H, $C\underline{H}CH_2$), 7.09 (s, 1H, H-6 thymine), 9.94 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) -3.42 (CH_3Si), 12.18 (CH_3 thymine), 49.75 (CH_2N), 54.81 (CH_2O), 110.90 (C-5 thymine), 132.37 (CHSi), 139.85 (C-6 thymine), 142.07 ($\underline{C}HCH_2$), 151.22 (C-2 thymine), 164.44 (C-4 thymine); MS (FAB) m/e 223.4 (100) [M-22]+, 255.4 (100) [M+1]+, 237.4 (76) [M-14] exact: 254.2.
7. Compound **1b**, ^{1}H NMR ($CDCl_3$+CD_3OD) 0.05 (s, 3H, CH_3Si), 1.68 (s, 3H, CH_3 thymine), 3.39 (s, 4H, $C\underline{H}_2OH$), 4.28-4.31 (d, 2H, J = 6.2 Hz, CH_2N), 5.61-5.68 (d, 1H, J = 14 Hz, CHSi), 6.11-6.25 (m, 1H, $C\underline{H}CH_2$), 7.12 (s, 1H, H-6 thymine); ^{13}C NMR($CDCl_3$) -6.77 (CH_3Si), 11.84 (CH_3 thymine), 50.10 (CH_2N), 52.65 (CH_2OH), 110.80 (C-5 thymine), 129.06 (CHSi), 140.64 (C-6 thymine), 143.73 ($\underline{C}HCH_2$), 151.43 (C-2 thymine), 164.40 (C-4 thymine); MS (FAB) m/e 255.7 [M-15]+, 271.4 [M+1]+, exact: 270.1.
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11. Compound **2a**. ^{1}H NMR ($CDCl_3$) 0.01 (s, 6H, CH_3Si), 1.80 (s, 3H, CH_3 thymine), 2.46 (s, 1H, OH), 3.31 (s, 2H, CH_2O), 4.26-4.28 (d, 2H, J= 6Hz, CH_2N), 5.68-5.77 (d, 1H, J= 19 Hz, CHSi), 5.98-6.07 (dt, 1H, J= 19 Hz, $C\underline{H}$=CHSi), 6.91 (s, 1H, H-6 thymine), 10.24 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) 5.02 (CH_3Si), 12.19 (CH_3 thymine), 51.79 (CH_2N), 54.46 (CH_2O), 110.76 (C-5 thymine), 130.62 (CHSi), 140.26 (C-6 thymine), 140.65 ($C\underline{H}$=CHSi), 151.15 (C-2 thymine), 164.76 (C-4 thymine).
12. Compound **3a**. ^{1}H NMR ($CDCl_3$) 0.10 (s, 6H, CH_3Si), 1.83 (s, 3H, CH_3 thymine), 2.60 (s, 1H, OH), 3.40 (s, 2H, CH_2O), 4.41 (s, 2H, CH_2N), 5.51-5.55 (m, 2H, CH2=), 6.93 (s, 1H, H-6 thymine), 10.11 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) -5.42 (CH_3Si), 12.19 (CH_3 thymine), 51.83 (CH_2N), 54.06 (CH_2Si), 110.67 (C-5 thymine), 127.50 (CH_2=), 140.41 (C-6 thymine), 144.11 ($\underline{C}$=CH_2), 151.24 (C-2 thymine), 164.67 (C-4 thymine); MS (FAB) m/e 255.1 (95) [M+1]+, 223.0 (100) [M-31]+, exact: 254.3.
13. Compound **3b**. ^{1}H NMR ($CDCl_3$+CD_3OD) 0.02 (s, 3H, CH_3Si), 1.72 (s, 3H, CH_3 thymine), 3.38 (s, 4H, CH_2O), 4.31 (s, 2H, CH_2N), 5.44-5.47(m, 2H, CH_2=), 6.93 (s, 1H, H-6 thymine); ^{13}C NMR ($CDCl_3$+CD_3OD) -8.94 (CH_3Si), 11.64 (CH_3 thymine), 51.72 (CH_2Si), 110.43 (C-5 thymine), 127.61 (CH_2=), 140.92 (C-6 thymine), 141.68 ($\underline{C}$=CH_2), 151.17 (C-2 thymine), 164.93 (C-4 thymine); MS (FAB) m/e 271.4 (100) [M+1]+, 293.3 (93) [M+23]+; HRMS (FAB+) found: 271.111157 exact: 271.111411.