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Synthesis of cyclonucleosides having a C–C bridge

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Contents

1. Introduction

Natural nucleosides are of great biological importance in metabolic pathways.[1,2] The typical structure of nucleosides has two molecular fragments: D-*ribo*- or D-2′-deoxyribopentofuranose as the sugar moiety and a purine or pyrimidine aglycone. These two moieties are covalently bonded from N_1 of pyrimidine (uracil, thymine and cytosine) or N_9 of purine (adenine and guanine) to $C_{1'}$ of the glycone in a β-configuration (Fig. 1).

The molecular geometry of nucleosides induces different conformations, which usually involve the determination of three principal structural parameters:[3] (i) the glycosyl torsion angle χ ($O_{4'}$-$C_{1'}$-N_9-C_4 for a purine nucleoside and $O_{4'}$-$C_{1'}$-N_1-C_2 for a pyrimidine nucleoside), which determines the *syn* or *anti* disposition of the nucleobase relative to the sugar moiety (*syn* when the C_2 carbonyl of pyrimidines or N_3 of purines lies over the sugar ring and *anti* for the opposite direction); (ii) the torsion angle γ ($O_{5'}$–$C_{5'}$–$C_{4'}$–$C_{3'}$), which determines the position of the 5′-OH relative to the $C_{3'}$ carbon atom (+*sc*, *ap*, −*sc* rotamers); and (iii) the phase angle of pseudorotation *P* (0–360°) and the maximum out-of-plane pucker υ_{max} (0–50°), which determine the puckering of the furanose ring and its deviation from planarity, respectively.[4,5] The value of *P* depends up on the five endocyclic sugar torsion angles (υ_0–υ_4) and on the puckering of the furanose ring. The conformation of the furanose ring around the pseudorotational cycle alternates every 18° between the envelope (E) and twist (T) form. The conformations of the nucleoside described by these three-state models (χ, γ, *P*) are in interdependent equilibria determined by steric and

Abbreviations: Ac, acetyl; AIBN, azobisisobutyronitrile (2,2′-azobis(2-methylpropionitrile)); An, anisyl; BOM, benzyloxymethyl; Bu, butyl; Bz, benzoyl; CAN, ceric ammonium nitrate; DBU, diazadicycloundecane; DCC, dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DNA, deoxyribonucleic acid; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; Et, ethyl; HMDS, 1,1,1,3,3,3-hexamethyldisilazane; imid, imidazol-1-yl; *i*-Pr, isopropyl; LDA, lithium diisopropylamide; LiHMDS, lithium hexamethyldisilazide; Me, methyl; Ms, mesyl; nd, non determined; NCS, *N*-chlorosuccinimide; NMO, *N*-methylmorpholine-*N*-oxide; PMB, *p*-methoxybenzyl; Ph, phenyl; PMHS, polymethylhydrosiloxane; PTSA, *p*-toluenesulfonic acid; pyr, pyridine; qt, quantitative; RNA, ribonucleic acid; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; *t*-Bu, *tert*-Butyl; THF, tetrahydrofuran; Thf, tetrahydrofuranyl; TIPDS, tetraisopropyldisilyloxane; TMS, trimethylsilyl; Ts, tosyl; TTMSS, tris(trimethylsilyl)silane.

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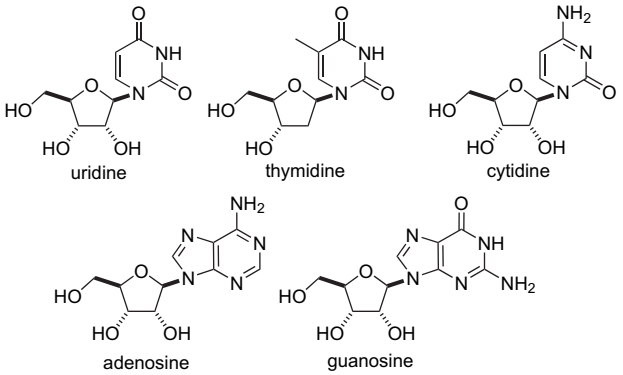


Figure 1. Classical natural nucleosides.

stereoelectronic effects (e.g., anomeric and *gauche* effects)[6] and the energy barriers between the preferred conformational states are usually low (Fig. 2).

In an enzymatic reaction, the problem is to correlate the conformational preference demanded by the specific enzyme in the activation pathway with a particular nucleoside conformation because the nucleoside conformation in solution can differ sharply from that determined in the solid state. Consequently, any conformation–activity study based exclusively on solid-state conformational parameters would be flawed, unless both solution and solid-state conformations are known to be equivalent. One strategy for pre-organising the nucleoside conformation might be to rigidify the normally flexible nucleoside by chemical modification. To overcome this problem, the limitation of conformation of a nucleoside or nucleotide is widely used to reach a particular conformation of a rotamer to study: (i) the affinity of a biomacromolecule for its natural ligand;[7] and (ii) the molecular recognition in an oligonucleotide chain (RNA/DNA).[8] This particular conformation can be predetermined by limiting the conformational equilibrium (*syn* or *anti*, North or South, $+sc$, *ap* or $-sc$) by the elaboration of restricted polycyclic structures. Nucleosides with a restricted conformation can be classified into three families: (i) *bicyclonucleosides* obtained by bonding two atoms of the furanose moiety via an alkylene unit or analogue; (ii) *cyclic phosphoesters* obtained by forming an alkylene bridge or analogue between the phosphorus atom and the nucleobase or the furanose moiety; and (iii) *cyclonucleosides* obtained by bonding one atom of the furanose moiety and one atom of the nucleobase via an alkylene unit or analogue (Fig. 3).

For the sake of clarity, this review has been arranged to describe the synthesis of cyclonucleosides having an alkylene group between the glycone moiety and the nucleobase.

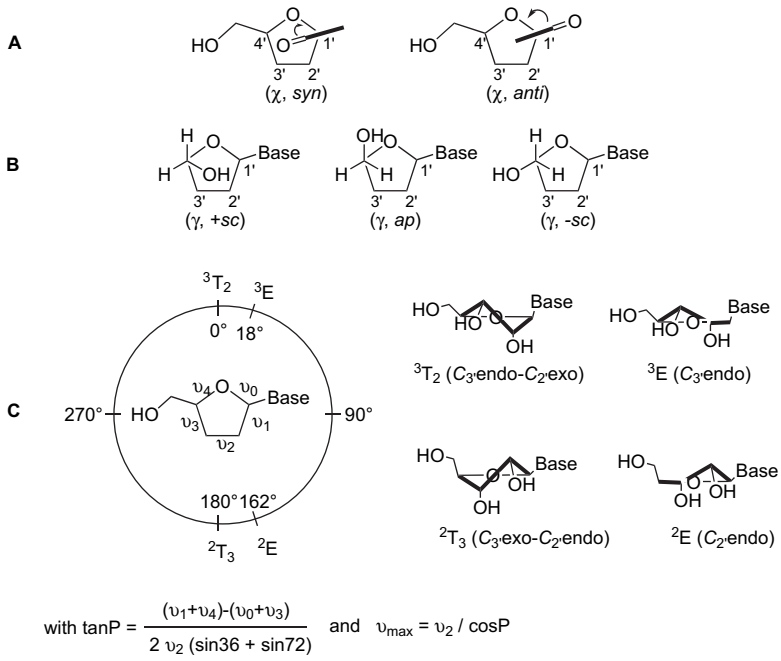


Figure 2. (A) Definition of *anti* and *syn* conformations for a pyrimidine nucleoside. (B) Definition of the torsion angle ranges for the $C_{4'}$–$C_{5'}$ bond. (C) Pseudorotational cycle of the furanose ring in a nucleoside (E=envelope and T=twist).

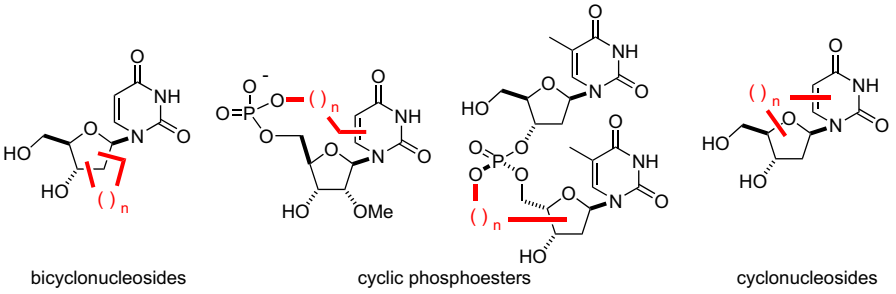


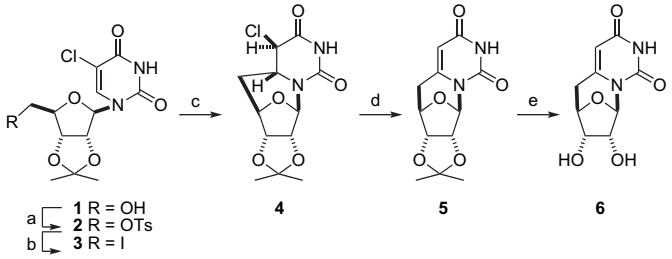
Figure 3. Different families of nucleoside analogues having a restricted conformation.

2. Synthesis of cyclonucleosides having a C–C bridge

2.1. Radical reactions

The synthesis of cyclonucleosides has been reported by the generation of a radical using chemical and photochemical initiation. In the first case, the formation of a radical at a position of the glycone moiety and intramolecular radical addition at a carbon atom of the nucleobase were described. In the second case, the formation of a radical at either a position of the glycone moiety or the nucleobase followed by intramolecular radical addition was developed.

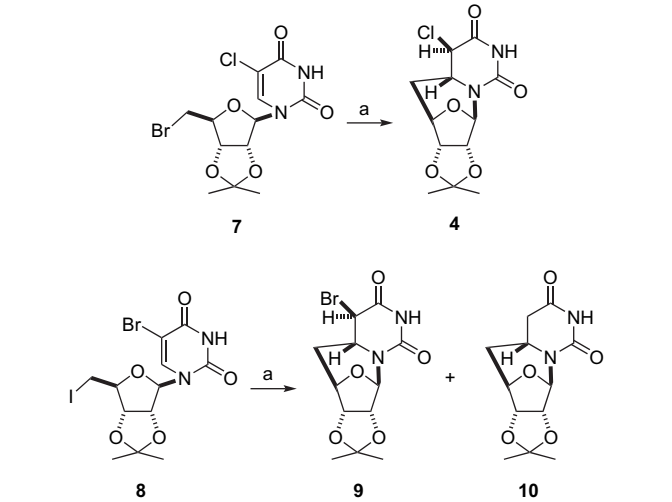
Ueda et al.[9] reported the synthesis of 6,5′-*cyclo*-5′-deoxyuridine (**6**) starting from the 5-chloro derivative **1** (Scheme 1). After tosylation of the primary hydroxyl group of compound **1**, iodination of the tosylate **2** furnished the 5′-iodo derivative **3** in 45% yield (two steps). Treatment of compound **3** with Bu_3SnH and AIBN afforded the cyclonucleoside **4** in 78% yield. The configuration of the protons H_5 and H_6 of compound **4** was trans and the cyclisation was a stereospecific cis-addition. Treatment of compound **4** with sodium ethoxide in ethanol and subsequent deprotection of the diol in **5** gave the corresponding 6,5′-cyclonucleoside **6** in 67% yield (two steps).



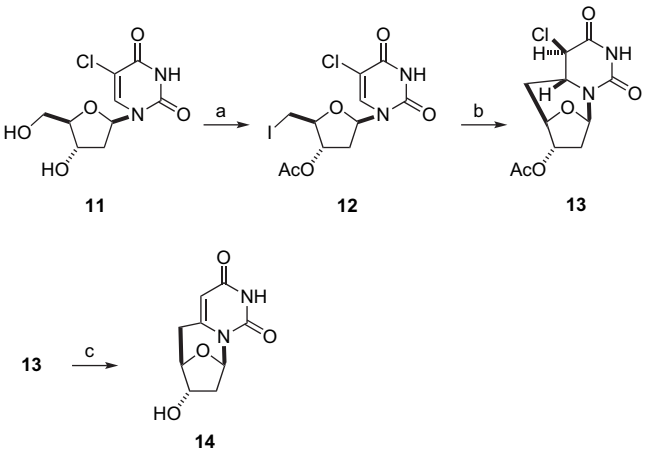
Scheme 1. Reagents and conditions: (a) TsCl, pyr (56%); (b) NaI, 2-butanone (80%); (c) Bu_3SnH, AIBN, benzene (78%); (d) NaOEt, H_2O, EtOH (88%); (e) HCl, H_2O, MeOH (87%).

It was notable that, starting from the 5′-deoxy-5′-bromo derivative **7**, the radical cyclisation afforded a lower yield (53 vs 78%)[9–11] and the use of the 5-bromouridine analogue **8** also gave a lower yield (40 vs 78%), probably due to over-reduction of the cyclodihydro-5-bromouridine intermediate **9** by Bu_3SnH during the radical cyclisation process, leading to compound **10** (Scheme 2).[9]

Application of the above strategy was described by Ueda et al. for the synthesis of the 6,5′-cyclonucleoside **14** starting from the 5-chloro-2′-deoxyuridine (**11**).[12] Compound **11** was converted into the 5′-iodo derivative **12** via selective iodination and subsequent acetylation of the free hydroxyl group. Cyclisation of **12** by the addition of Bu_3SnH and AIBN in toluene afforded the desired 5-chloro intermediate **13** in 75% yield. Treatment of nucleoside **13** with sodium methoxide in methanol gave the corresponding cyclonucleoside **14** (Scheme 3).

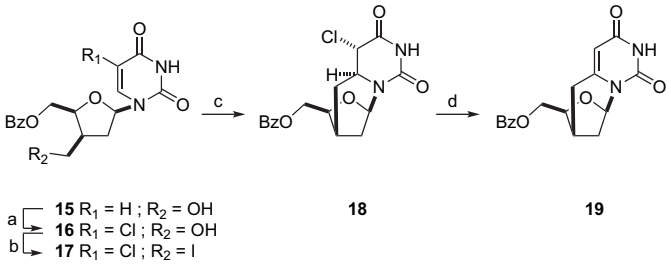


Scheme 2. Reagents and conditions: (a) Bu_3SnH, AIBN, benzene (for **4**: 53%; for **9**: 40%).



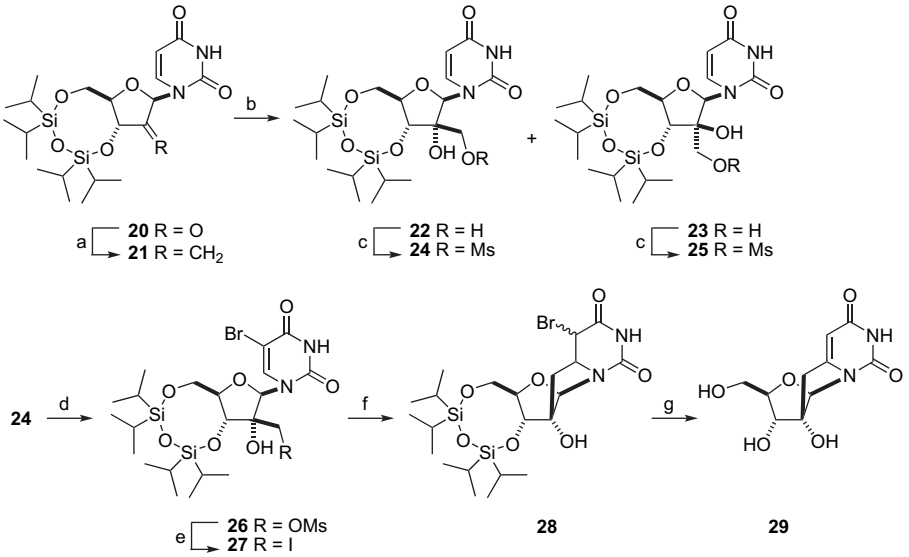
Scheme 3. Reagents and conditions: (a) (1) PPh_3, I_2, DMF; (2) Ac_2O, DMAP, MeCN (35%); (b) Bu_3SnH, AIBN, toluene (75%); (c) MeONa, MeOH (80%).

Ueda et al. reported the synthesis of the 6,3′-methanocyclouridine **19** starting from the 3′-hydroxymethyl derivative **15**.[13] Multistep conversion of uridine into 3′-hydroxymethyl derivative **15** and then chlorination and subsequent iodination of compound **16** afforded the iodide derivative **17**. The radical cyclisation between the 6- and 3′-position of compound **17** was performed by the addition of Bu_3SnH in the presence of AIBN in benzene to furnish stereospecifically the corresponding 5(*S*),6(*S*)-cyclodihydro nucleoside **18** in 68% yield. Treatment of nucleoside **18** with DBU in benzene gave the target protected cyclonucleoside **19** in 67% yield (Scheme 4).



Scheme 4. Reagents and conditions: (a) NaOAc, AcOH, DMF, Cl_2 (62%); (b) (1) TsCl, DMAP, pyr; (2) LiI, butan-2-one (57%, two steps); (c) Bu_3SnH, AIBN, benzene (68%); (d) DBU, benzene (67%).

Ueda et al. described the synthesis of the 6,2′-methanocyclouridine (**29**) starting from the 2′-keto nucleoside **20**.[14] Wittig homologation of the starting material furnished the 2′-deoxy-2′-methyleneuridine **21** in 58% yield (Scheme 5). Dihydroxylation of the alkene **21** with OsO_4 and NMO afforded a mixture of 2-hydroxymethyluridine **22** and its arabinosyl isomer **23** (4:1) in 92% yield. The mixture of compounds **22** and **23** was then mesylated leading to **24** and **25**, and the 2′(*R*)-isomer **24** was separated in 55% yield. After bromination of nucleoside analogue **24** at the C-5 position and subsequent iodination of compound **26**, the 2′(*R*)-iodomethyl derivative **27** was reacted with Bu_3SnH in the presence of AIBN to yield the corresponding 6,2′-cyclonucleoside **28** in 32% yield. Treatment of compound **28** with DBU and then with TBAF furnished the target cyclonucleoside **29** in 62% yield (two steps).

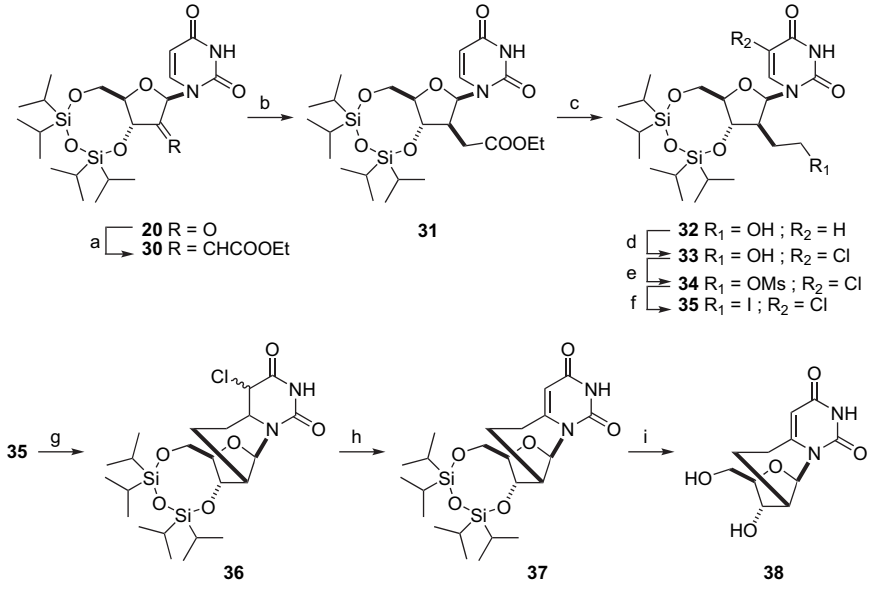


Scheme 5. Reagents and conditions: (a) NaH, $MePh_3PBr$, DMSO, THF (58%); (b) $Et_4N^+OH^-$, *t*-BuOOH, OsO_4, *t*-BuOH, THF (80%); (c) MsCl, pyr (55%); (d) AcONa, AcOH, Br_2 (88%); (e) LiI, butan-2-one (60%); (f) Bu_3SnH, AIBN, benzene (32%); (g) (1) DBU, benzene (71%); (2) TBAF, THF (88%).

Ueda et al. reported the synthesis of 6,2′-ethanocyclouridine having a spacer of two carbon atoms between the glycone and nucleobase.[15,16] Starting from the 2′-keto nucleoside **20**, treatment with $Ph_3PCHCOOEt$ afforded the desired α,β-unsaturated ester **30** in 98% yield. Stereospecific reduction of compound **30** with $NaBH_4$ in ethanol and subsequent treatment with $LiBH_4$ furnished the 2′(*S*)-hydroxyethyl derivative **32** in 34% yield (two steps). After chlorination at the C-6 position and iodination of compound **33** via the corresponding mesylate **34**, leading to compound **35**, the radical cyclisation with Bu_3SnH in the presence of AIBN afforded the corresponding cyclonucleoside **36** in 29% yield (three steps). Dehydrochlorination of compound **36** with DBU in benzene and deprotection of the cyclonucleoside analogue **37** gave the target 6,2′-ethanocyclonucleoside **38** in 68% yield (two steps) (Scheme 6).

Ueda et al.[17] described the synthesis of 8,2′-ethano-*cyclo*-2′-deoxyadenosine (**40**) via the corresponding 2′-iodoethyl derivative **39** using the above strategy (Fig. 4).

Ueda et al.[18,19] reported the synthesis of a *syn*-fixed cyclonucleoside starting from a ketose (Scheme 7). Moffatt oxidation of D-fructose derivative **41** and subsequent homologation with $Ph_3PCHCOOEt$ furnished the α,β-unsaturated ester **42** in 85% yield (two steps). Conversion of compound **42** into the triesters **43** by treatment with Bz_2O in the presence of TBAF and then acid hydrolysis of the *O*-2,2′-anhydro derivative **43** followed by acetylation afforded the tetraesters **44** in 69% yield (three steps). After hydrogen transfer reduction of compound **44** with PMHS as a hydrogen donor over Pd/C and subsequent deprotection of the 3′- and 5′-hydroxyl groups, silylation using Markiewicz methodology furnished the ester **45** in 72% yield. Classical inversion of the 2′-hydroxyl group was carried on via successive Robins oxidation and $NaBH_4$ reduction to furnish the *ribo*-derivative **46** in 72% yield. The ribonucleoside **46** was the major product because the C-1′ and C-3′ substituents of compound **46** blocked the α-face more efficiently compared to the base moiety at the C-1′ position for the β-face. Desilylation of the diol, isopropylidenation and silylation of the



Scheme 6. Reagents and conditions: (a) $Ph_3PCHCOOEt$, CH_2Cl_2 (98%); (b) $NaBH_4$, EtOH (58%); (c) $LiBH_4$, THF (58%); (d) *N*-chlorosuccinimide, DMF, AcOH (56%); (e) MsCl, pyr (86%); (f) LiI, butan-2-one (65%); (g) Bu_3SnH, AIBN, benzene (94%); (h) DBU, benzene (73%); (i) TBAF, THF (93%).

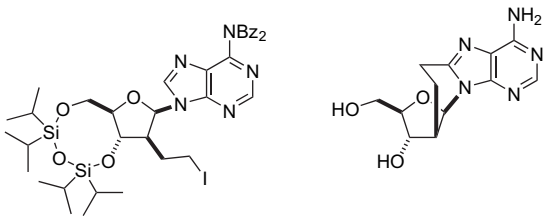
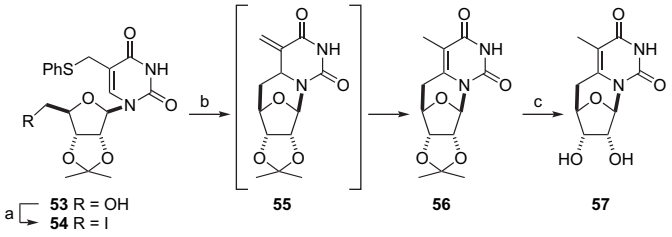


Figure 4. Iodide intermediate **39** and cyclonucleoside **40**.

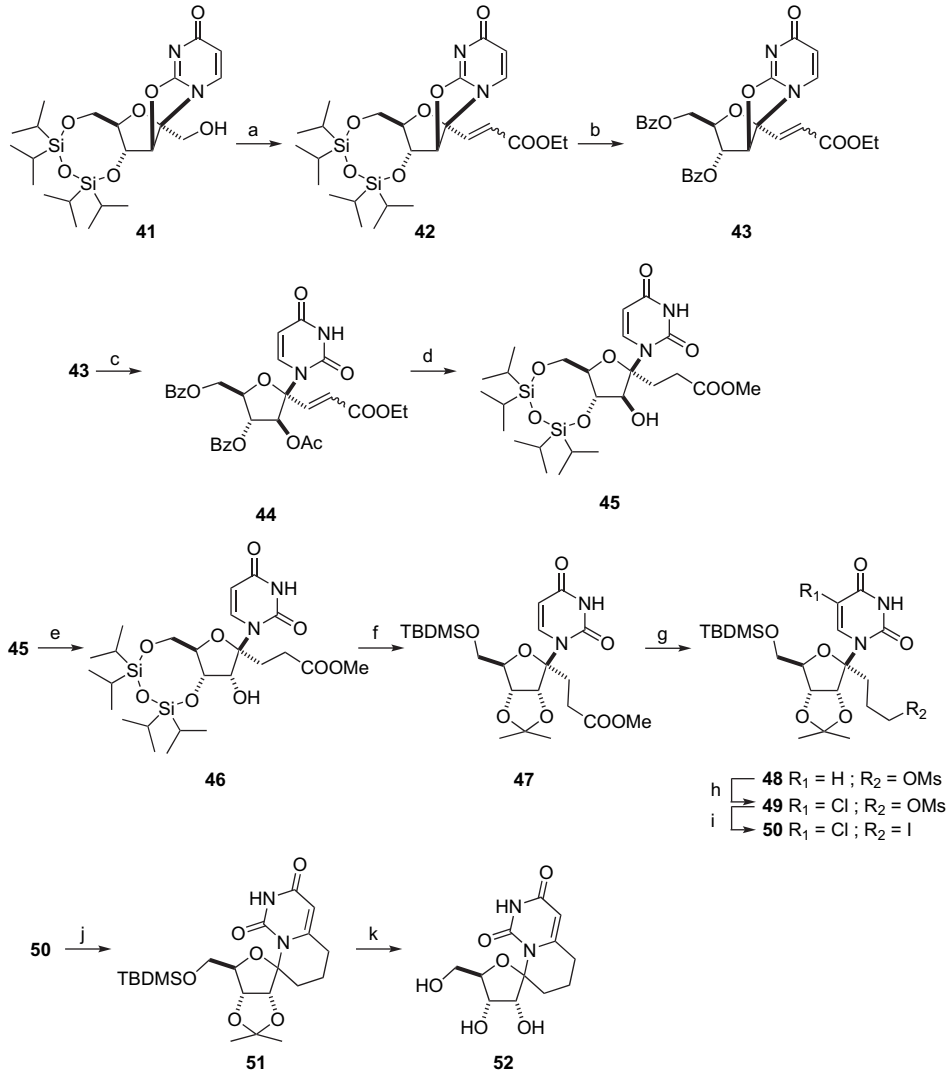
primary hydroxyl group gave the nucleoside **47** in 59% yield (three steps). After reduction of the ester **47** and mesylation, chlorination at the C-5 position of nucleoside analogue **48** by *N*-chlorosuccinimide afforded the nucleoside analogue **49** in 56% yield (three steps). Iodination of compound **49** with lithium iodide in butan-2-one and radical cyclisation of iodide derivative **50** with Bu_3SnH in the presence of AIBN in benzene and an elimination reaction with DBU furnished the cyclonucleoside **51** in 58% yield (three steps). Classical deprotection of the triol in two steps furnished the target nucleoside **52** in 61% yield (two steps).

Ueda et al.[12] and Hsu et al.[20] reported the synthesis of a 5′,6-cyclonucleoside having a methyl group in 5-position. Starting from the 5-phenylthiomethyluridine derivative **53**, successive mesylation and iodination afforded the thioether **54** in 94% yield. Treatment of compound **54** with Bu_3SnH in the presence of AIBN in toluene gave the cyclonucleoside **56** in 74% yield via an addition–β-elimination process, without detection of the presumed intermediate **55**. Classical deprotection afforded the target nucleoside **57** in 93% yield (Scheme 8).

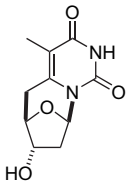
Application of this strategy permitted 2′-deoxy nucleoside **58** to be obtained (Fig. 5).[12]



Scheme 8. Reagents and conditions: (a) (1) MsCl, pyr; (2) NaI, butan-2-one (94%, two steps); (b) Bu_3SnH, AIBN, toluene (74%); (c) CF_3COOH (93%).



Scheme 7. Reagents and conditions: (a) (1) DCC, CF_3COOH, pyr, DMSO, benzene; (2) $Ph_3PCHCOOEt$, CH_2Cl_2 (85%); (b) Bz_2O, TBAF, THF (96%); (c) (1) HCl 2 N, DMF; (2) Ac_2O, DMAP pyr (72%); (d) (1) PMHS, Pd/C, EtOH (92%); (2) MeONa, MeOH; 3. 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, DMF, pyr (78%, two steps); (e) (1) CrO_3, pyr, 4 Å molecular sieves, CH_2Cl_2; (2) $NaBH_4$, MeOH (72%, two steps); (f) (1) TBAF, THF; (2) 2,2-dimethoxypropane, $HClO_4$, acetone; (3) TBDMSCl, *i*-Pr_2EtN, DMF (59%, three steps); (g) (1) $LiBH_4$, THF; (2) MsCl, pyr (67%); (h) NCS, AcOH (83%); (i) LiI, butan-2-one (79%); (j) (1) Bu_3SnH, AIBN, benzene; (2) DBU, benzene (74%); (k) (1) TBAF, THF; (2) HCl 1 N, THF (61%).



58

Figure 5. Cyclonucleoside **58**.

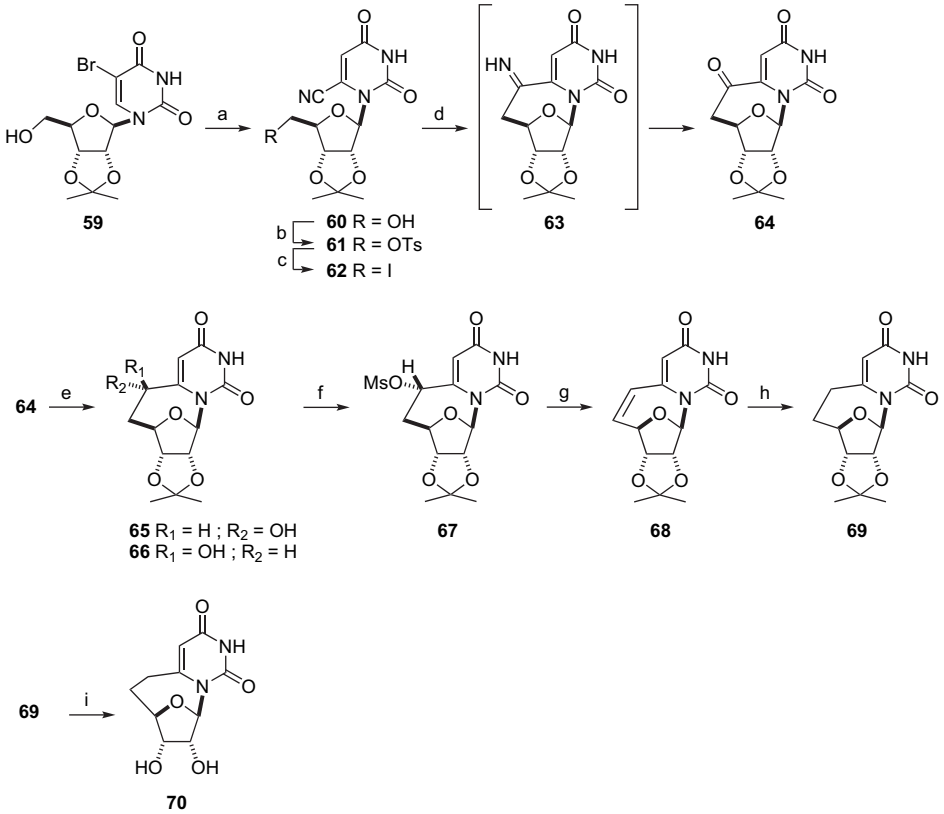
Ueda et al.[21] described the synthesis of 6,6′-*cyclo*-5′,6′-dideoxyhexofuranosyluracil (**70**) via the radical cyclisation of a 6-cyanouridine derivative. Starting from the 5-bromo derivative **59**, treatment with NaCN in DMF gave the cyano compound **60** in 76% yield. After tosylation and iodination of the primary hydroxyl group via the corresponding tosylate **61**, the nucleoside analogue **62** was subjected to radical cyclisation with Bu_3SnH in the presence of AIBN in toluene to give the imine **63**. Without purification, compound **63** was reacted with aqueous acetic acid to furnish the ketone **64** in 35% yield. The low yield was explained by the competitive formation of the 5′-deoxy nucleoside. Reduction of the ketone **64** with $NaBH_4$ in methanol afforded a mixture of two diastereoisomers **65** and **66** in 40 and 24% yield. Mesylation of the 6′(*S*)-hydroxy nucleoside **65** and treatment of **67** with DBU in dioxane afforded the corresponding alkene **68** in 59% yield. Hydrogenation of compound **68** and deprotection of the diol in **69** furnished the target nucleoside **70** in 72% yield (Scheme 9).

The synthesis of 8,2′-ethanocycloadenosine (**77**) was reported by Burger et al. via the 8-vinyladenosine derivative **76**.[22] Starting from the protected adenosine **71**, lithiation at the C-8 position of the purine with LDA in THF and quenching with iodine yielded the 8-iodo derivative **72** in 72% yield. Heating of compound **72** with $Bu_3SnCHCH_2$ in the presence of $Pd(PPh_3)_4$ in DMF gave the 8-vinyl nucleoside **73** in 92% yield. After deprotection of the triol and silylation of the diol **74** using the Markiewicz reagent, compound **75** was reacted with PhOCSCl to furnish the thiocarbonyl derivative **76**. Generation of the radical at C-2′ was effected by the addition of Bu_3SnH in the presence of AIBN in toluene to afford the 6-*endo* product **77** in 65% yield (Scheme 10).

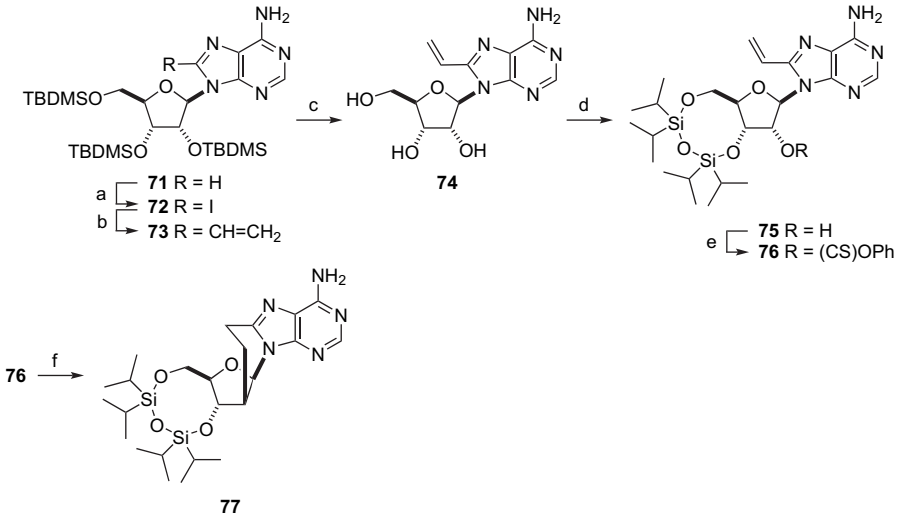
Chatgilialoglu et al. reported the synthesis of 5′,8-*cyclo*-2′-deoxyadenosine via the corresponding 5′-aldehyde.[23] Starting from the protected adenosine derivative **78**, Moffatt oxidation of the primary hydroxyl gave the aldehyde **79** in 80% yield. Compound **79** was treated with $(TMS)_3SiH$ and 1 equiv of AIBN in fluorobenzene and gave a mixture of 5′(*S*)-cyclonucleosides **80** and **81** in a 1:1 ratio. Oxidation of compound **80** to the adenosine derivative **81** was accomplished by the addition of tetrachloro-1,4-benzoquinone (chloranil) in xylene in quantitative yield (Scheme 11).

The authors proposed that the cyclonucleosides **80** and **81** were obtained via the aminyl radical **83**.[23] Addition of a $(TMS)_3Si$ radical to the aldehyde **79** afforded the C-5′ radical **82** that attacked the adenine moiety intramolecularly to give the aminyl radical **83**. The radical **83** was nearly planar and the stereospecificity of the cyclisation was due to the exclusive formation of the chair conformation in the ring that was formed. Hydrogen abstraction from the aminyl radical **83** gave the derivative **80** and addition of the radical generated from the decomposition of AIBN gave the derivative **81** (Scheme 12). It was noteworthy that Chatgilialoglu et al. described the same strategy in 2006 using Bu_3SnH instead of $(TMS)_3SiH$.[24]

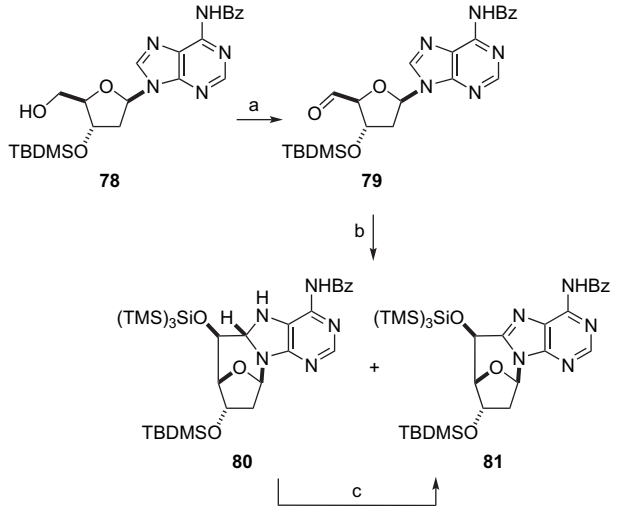
In 2006, Chatgilialoglu et al. described the synthesis of the cyclonucleosides **90**–**93** via radical cyclisation generated by 1,6-radical translocation (1,6-RT).[24] Starting from the 8-bromoadenosine derivative **84**, treatment with $(TMS)_3SiH$ in the presence of AIBN in fluorobenzene afforded the corresponding C-8 radical **85** through bromine atom abstraction by silyl radicals. The radical **85**



Scheme 9. Reagents and conditions: (a) NaCN, DMF (76%); (b) TsCl, pyr (78%); (c) NaI, butan-2-one (88%); (d) (1) Bu_3SnH, AIBN, toluene; (2) AcOH, H_2O, THF (35%); (e) $NaBH_4$, MeOH (for **65**: 40%; for **66**: 24%); (f) MsCl, pyr (79%); (g) DBU, dioxane (59%); (h) H_2, Pd/C, THF (82%); (i) HCl 1 N, MeOH (88%).



Scheme 10. Reagents and conditions: (a) LDA, THF, I_2 (72%); (b) $Bu_3SnCHCH_2$, $Pd(PPh_3)_4$, DMF (92%); (c) TBAF, THF (nd); (d) $(i\text{-}Pr_2SiCl)_2O$, pyr (nd); (e) PhOCSCl, DMAP, MeCN (nd); (f) Bu_3SnH, AIBN, toluene (65%).



Scheme 11. Reagents and conditions: (a) DCC, DMSO, $CHCl_2COOH$ (80%); (b) $(TMS)_3SiH$, AIBN, C_6H_5F (for **75**: 35%; for **76**: 35%); (c) chloranil, xylene (quant).

furnished the α-silyloxyl secondary carbon-centred radical **86** by 1,6-RT, and cyclisation of this latter radical gave the corresponding aminyl radicals **87** and **88** and the nucleoside analogue **89**. These aminyl radicals **87** and **88** afforded the target cyclonucleosides **90**–**93** and the nucleoside analogue **89** as a mixture in a 39:39:4:4 ratio (Scheme 13).

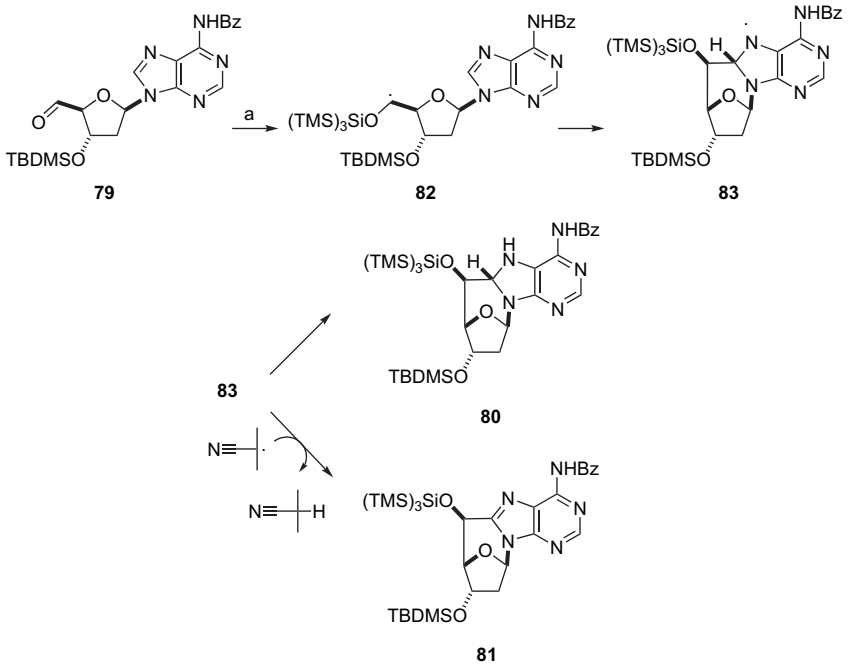
To complete this work, Chatgilialoglu et al. reported the above cyclisation reaction in the presence of oxygen and noted that complete conversion of the starting aldehyde **79** was observed with the exclusive formation of the cyclonucleoside **81** in 75% yield (Scheme 14).[23] The mechanism proposed by the authors is described in Scheme 14. The aminyl radical **83** was in resonance with the structure **94**, where the unpaired electron was placed at the C-4 position and addition to molecular oxygen afforded the peroxyl radical **95**. This radical **95** should undergo a facile hydrogen migration via the chair-type transition state **96** to generate the C-6 radical **97**, which eliminated the HOO$^{\bullet}$ radical, affording the target cyclonucleoside **81**. Hydrogen abstraction from silane by the HOO$^{\bullet}$ radical should regenerate the $(TMS)_3Si$ radical, completing this chain reaction.

Application of the radical 1,6-hydrogen transfer and cyclisation reaction permitted the synthesis of pyrimidine *C*-cyclonucleosides.[25] After protection of the uridine analogue **98** at the N-3 position with a *p*-methoxybenzyl (PMB) group, the 6-phenylseleno derivative **100** was obtained in 92% yield by treatment of compound **99** with LiHMDS in the presence of diphenyl diselenide. Compound **100** was treated with TTMSS in the presence of AIBN in toluene and gave the 5′-*S*-epimer **101** and the 5′-*R*-epimer **102** in 60 and 11% yield, respectively. Treatment of compound **101** with LiHMDS at −80 °C followed by $PhSO_2Cl$ afforded a diastereomeric mixture of cyclonucleosides **103**, which was further treated with DBU in 1,4-dioxane, producing the 6,5′-cyclonucleoside **104** (69%, two steps). Classical deprotection of the N-3 nitrogen atom under oxidative conditions and subsequent removal of the silyl group in **105** furnished the target cyclonucleoside **106** in 58% yield (two steps) (Scheme 15).

Takahata et al. proposed a reaction mechanism involving two possibilities (Scheme 16).[25] First, the C-6 radical intermediate **107**, formed as a result of the reaction of compound **100** with TTMSS and AIBN, led to a 1,6-hydrogen transfer to produce the C-5′ radical intermediate **108**. In order to explain the selectivity of the cyclisation, the authors proposed that the intermediate **108** adopted an *anti* conformation around the glycosidic bond with a trans orientation around the C-4′–C-5′ bond giving the 5′-*S*-epimer **101**. The second possibility was that the C-6 radical preferentially abstracted the pro-*S* hydrogen of C-5′, and the resulting intermediate **107** immediately cyclised to form the cyclonucleoside **101**.

Radical reactions using photochemistry for the synthesis of cyclonucleosides have also been reported. Irradiation was effected starting from nucleoside analogues having: (i) a thiophenyl group in different positions of the glycone moiety or nucleobase; (ii) a keto group in the 5′-position of the glycone moiety; and (iii) a bromine atom in the nucleobase. Cadet et al. described the synthesis of 8,5′-*cyclo*-2′,5′-dideoxyadenosine (**112**) via the corresponding 5′-phenylthio-2′,5′-dideoxyadenosine (**111**).[26] Starting from N_6-benzoyl-2′-deoxyadenosine (**109**), treatment with TsCl afforded the corresponding 5′-tosylate **110** and subsequent addition of PhSH in the presence of sodium methoxide gave the adenosine analogue **111** in 42% yield (two steps). Far-UV irradiation of a de-aerated acetonitrile solution of compound **111** in the presence of $P(OEt)_3$ as trapping agent for the released phenylthiyl radical gave the target cyclonucleoside **112** in 51% yield (Scheme 17).

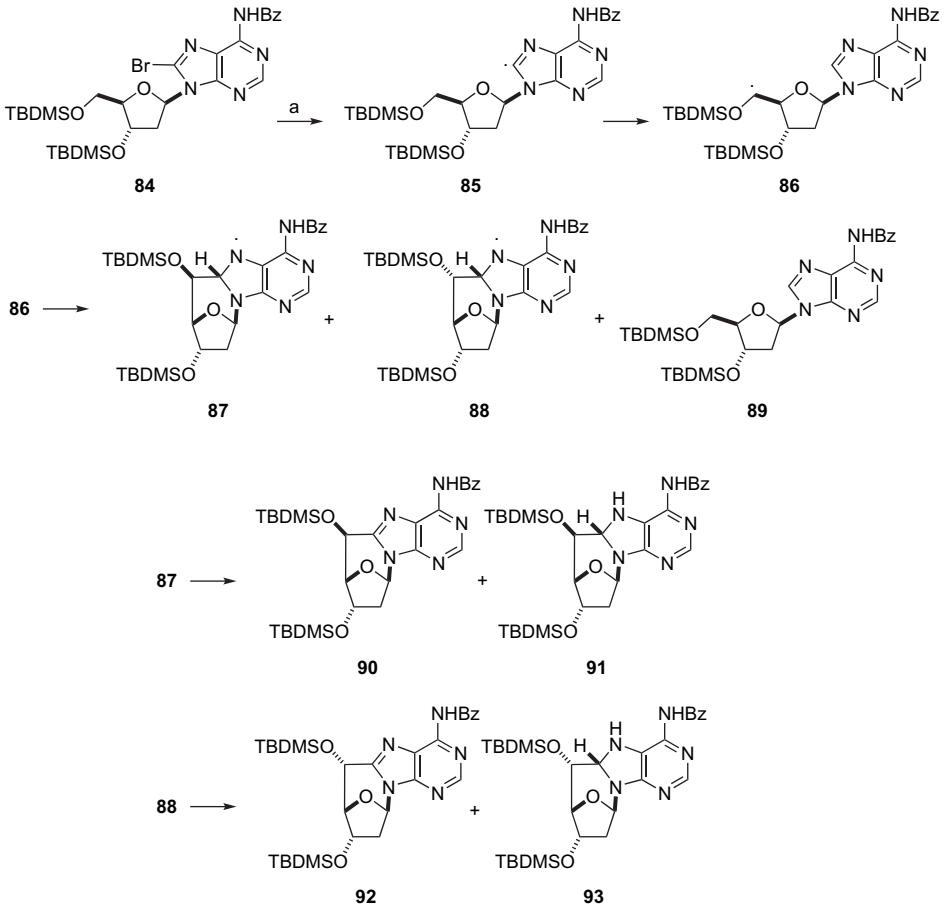
Two decades before, Matsuda et al. described the synthesis of the 5′-deoxy-8,5′-cycloadenosine (**115**) in 36% yield, starting from the corresponding 5′-deoxy-5′-thiophenyl derivative **113**.[27] Compound **113** was treated with $P(OEt)_3$ in acetonitrile and irradiated



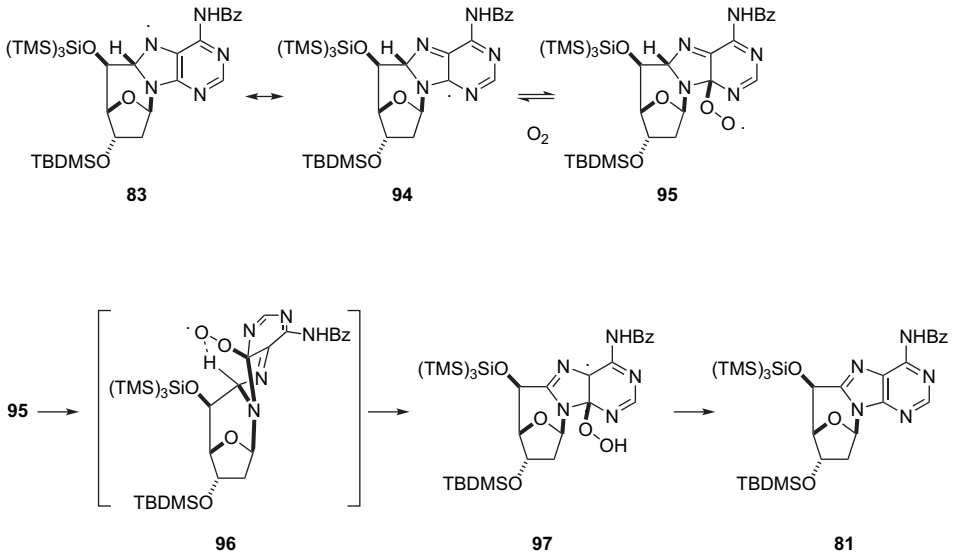
Scheme 12. Reagents and conditions: (a) $(TMS)_3SiH$, AIBN, C_6H_5F.

with a 60-W low-pressure Hg lamp to furnish, after deprotection of the diol **114**, the cyclonucleoside **115** in 36% yield (Scheme 18).

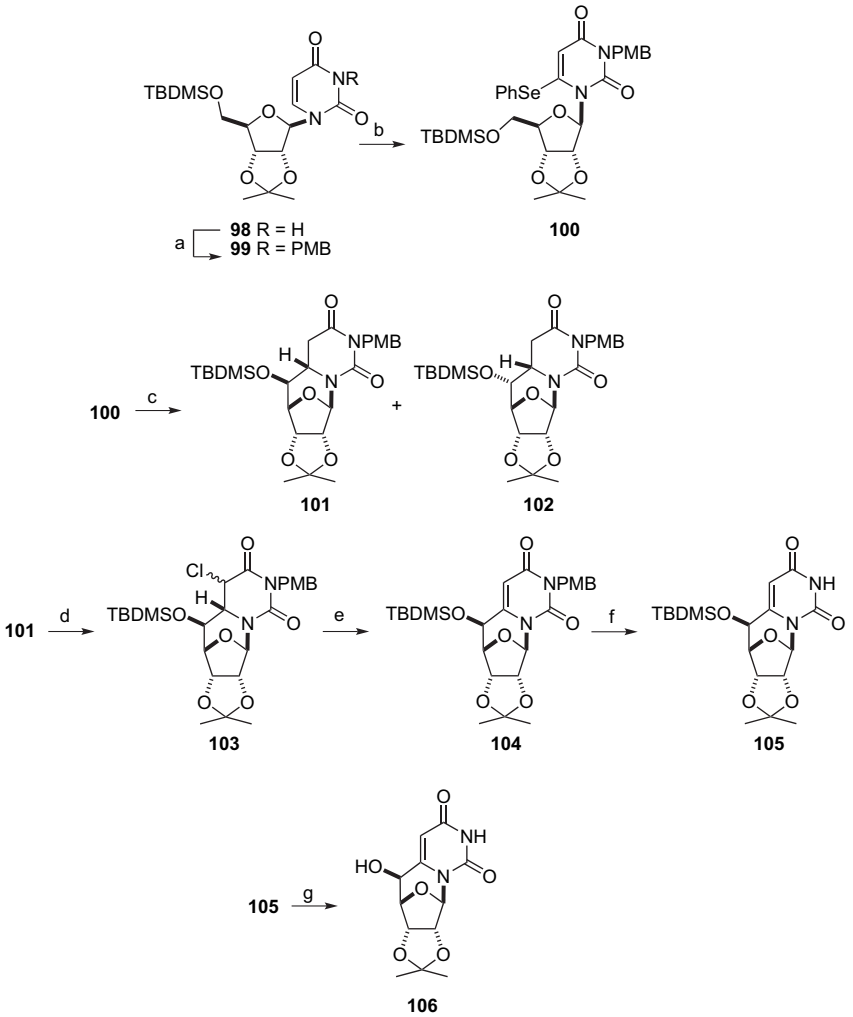
The authors proposed that the thiophenyl group in compound **113** was photo-activated initially, rather than the adenine moiety, to yield a 5′-methylene intermediate **116** and a thiophenyl radical.[27] The intermediate **116** cyclised to the next aminyl radical intermediate **117** followed by the release of an hydrogen radical to give the cyclonucleoside **114** (Scheme 19).



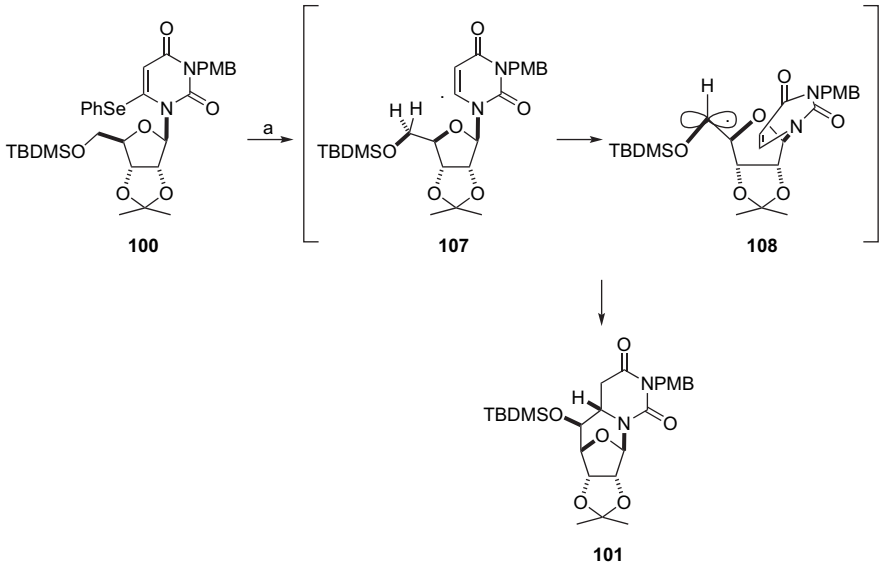
Scheme 13. Reagents and conditions: (a) $(TMS)_3SiH$, AIBN, C_6H_5F.



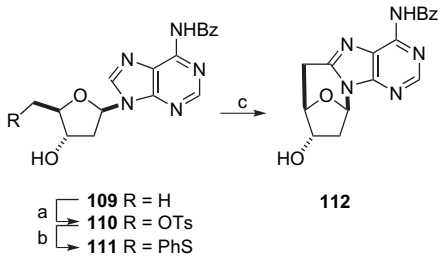
Scheme 14. Reagents and conditions: (a) $(TMS)_3SiH$, AIBN, O_2, C_6H_5F.



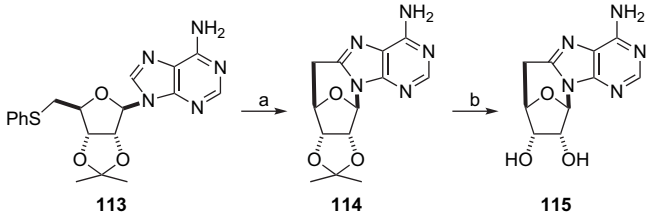
Scheme 15. Reagents and conditions: (a) PMBCl, DBU, DMF (97%); (b) $(PhSe)_2$, LiHMDS, THF (92%); (c) TTMSS, AIBN, toluene (for **101**: 60%; for **102**: 11%); (d) LiHMDS, THF, then $PhSO_2Cl$; (e) DBU, 1,4-dioxane (69%, two steps); (f) CAN, MeCN, H_2O (72%); (g) TBAF, THF (81%).



Scheme 16. Reagents and conditions: (a) TTMSS, AIBN, toluene.



Scheme 17. Reagents and conditions: (a) TsCl, pyr (82%); (b) PhSH, MeONa, MeOH (51%); (c) λ_{254}, $P(OEt)_3$, MeCN (51%).



Scheme 18. Reagents and conditions: (a) λ_{254}, $P(OEt)_3$, MeCN (51%); (b) HCl, H_2O (71%).

Somers et al. reported the synthesis of 8,5′-*cyclo*-2′,5′-dideoxyadenosine analogue using the same strategy, but with a different protecting group.[28] Starting from **118**, deprotection of the primary hydroxyl group furnished the silylated derivative **119**, which was converted into the corresponding 5′-thiophenyl analogue **120** in 95% yield. Compound **120** was submitted to photolysis at 254 nm in acetonitrile in the presence of $P(OMe)_3$ by irradiating with a 400-W medium-pressure mercury lamp to furnish the target nucleoside **121** in 50% yield (Scheme 20).

Application of this strategy was described by Ueda et al. for the synthesis of a 2′,8-cyclonucleoside **134**.[29] Starting from the adenosine derivative **122**, Wittig homologation furnished the alkene **123** in 15% yield. Compound **123** was hydroxylated by treatment with OsO_4 in the presence of NMO to furnish the two diols **124** and **125** with a trans addition to the base orientation. Next, classical conversion into the two 2′-phenylthiomethylguanosines **128** and **129** was effected by mesylation, leading to compounds **126** and **127**, and successive substitution with thiophenoxide in 23 and 21% yield (two steps). Photo-irradiation of compound **128** at 254 nm in the presence of trimethyl phosphite afforded the cyclonucleosides **130** and **131** in 67% yield. After deacetylation, desilylation and then reacetylation the diacetate **132** was subsequently treated with iodotrimethylsilane, formed in situ, to give compound **133**. Classical treatment of the analogue **133** with triethylamine in methanol furnished the target cyclonucleoside **134** in 20% yield (three steps) (Scheme 21).

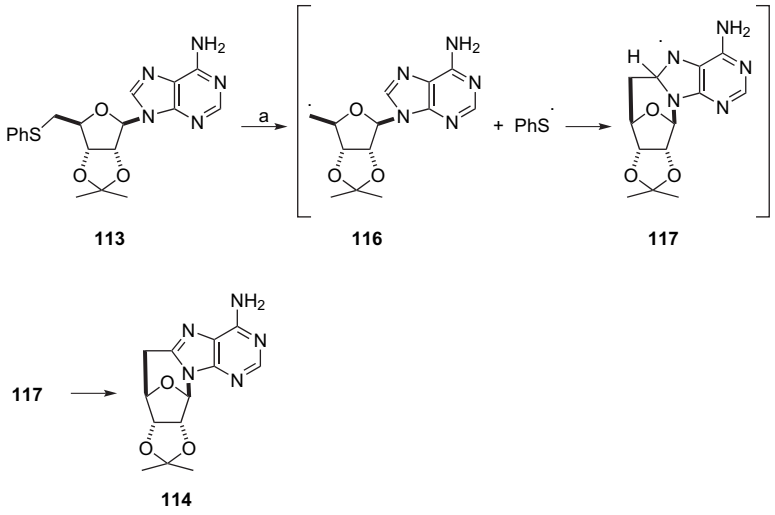
The above methodology has been used by Ueda's group to prepare **140**–**144** via the thiophenyl derivatives **135**–**139** (Table 1).

Ueda et al.[32] described the synthesis of 8,5′-cycloadenosine using photochemical cyclisation via the 8-phenylthioadenosine analogue. Starting from 2′,3′-*O*-isopropylidene-8-bromoadenosine (**145**), treatment with PhSNa in methanol gave the 8-phenylthioadenosine analogue **146** in 85% yield. Irradiation of compound **146** with a 400-W high-pressure Hg lamp in the presence of $P(OMe)_3$ afforded the 8,5′(*S*)-cycloadenosine **147**, the 8,5′(*R*)-cycloadenosine **148**, and the corresponding adenosine in 19, 10 and 6% yield, respectively. Classical deprotection of the compounds **147** and **148** gave the target cyclonucleosides **149** and **150** in high yields (Scheme 22).

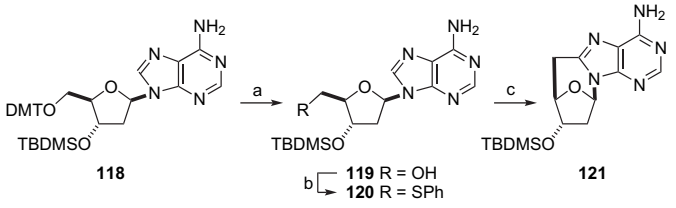
The cyclisation seen in the conversion of **146** into **147** and **148** is likely to be due to the formation of the radical intermediate **151** and a phenylthiyl radical and the subsequent formation of the biradical intermediate **152**, which afforded the cyclonucleosides **147** and **148**, as proposed by the authors (Scheme 23).

Recently, Chatgilialoglu et al.[33] reported the synthesis of 5-keto derivatives as photolabile precursors for the selective generation of the 5′-nucleosidyl radical. The starting nucleoside **153** was converted into the intermediate 5′-aldehyde **154** by applying a modification of the Moffatt oxidation procedure. The aldehyde **154** was reacted with TMSCN and ZnI_2 in the presence of 4 Å molecular sieves in CH_2Cl_2. Next, the crude product was immediately protected with TBDMSCl to furnish a mixture of the two diastereoisomers **155** and **156**. After crystallisation, compound **155** was isolated in 25% yield. *t*-BuLi addition to the nitrile **155** provided the corresponding imine **157** in 32% yield. Conversion of the imine **157** into the (5′*R*)-*tert*-butyl ketone **158** was effected in acidic media in 78% yield. The photolysis of **158** afforded the cyclonucleoside **159** in 20% yield and the 2′-deoxyguanosine **160** in 27% yield (Scheme 24).

The authors explained that the photolysis of the ketone **158** in the presence of BuSH gave selectively the corresponding 5′-radical



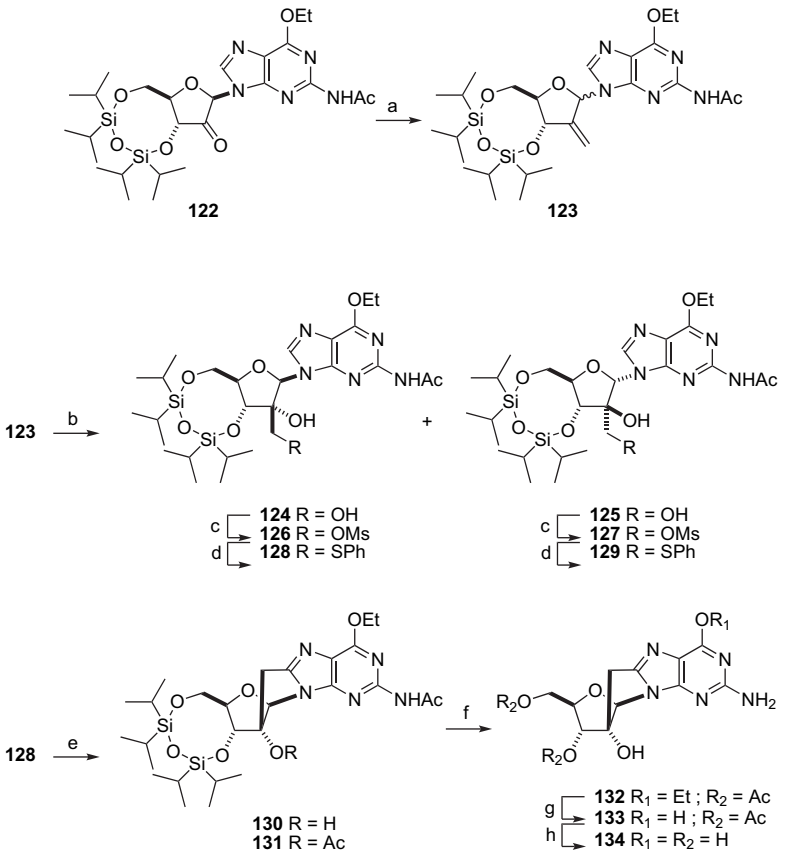
Scheme 19. Reagents and conditions: (a) λ_{254}, $P(OEt)_3$, MeCN (51%).



Scheme 20. Reagents and conditions: (a) I_2, MeOH (64%); (b) Ph_2S_2, $(n\text{-}Bu)_3P$, DMF (95%); (c) λ_{254}, $P(OMe)_3$, MeCN (50%).

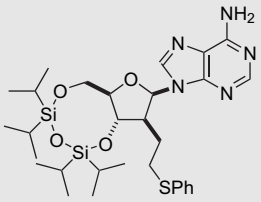
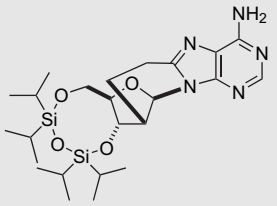
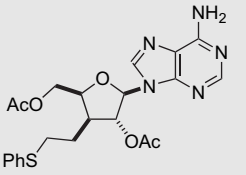
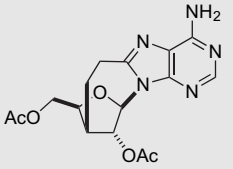
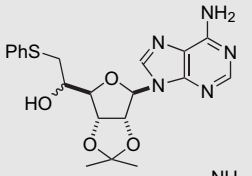
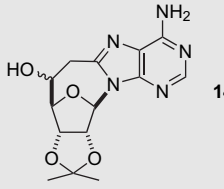
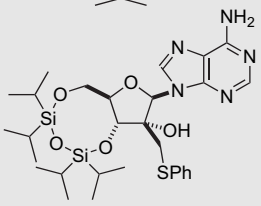
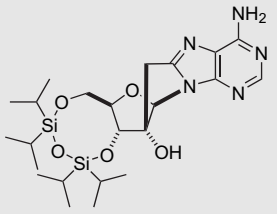
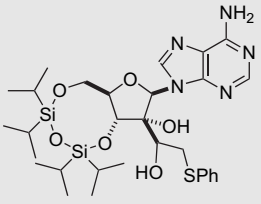
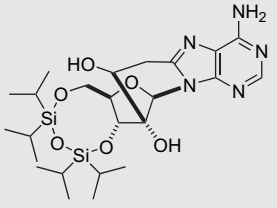
intermediate **161**, which is partitioned between two competitive reaction pathways: (i) a bimolecular reduction leading to the nucleoside **160**; and (ii) an intramolecular cyclisation onto the 8-position of the purine base, leading to radical **162** and subsequently to cyclonucleoside **159** (Scheme 25).[33]

Chatgilialoglu et al.[34] reported the same strategy, starting from 8-bromo-2′-deoxyadenosine (**163**). Photochemical irradiation, at 254 nm, of compound **163** in acetonitrile furnished the corresponding cyclonucleosides **164** and **165** in 41 and 24% yield, respectively (Scheme 26).



Scheme 21. Reagents and conditions: (a) CH_2PPh_3, THF, DMSO (15%); (b) OsO_4, NMO, *t*-BuOH, H_2O (for **124** and **125**: 77%); (c) MsCl, pyr; (d) *t*-BuOK, PhSH, DMF (23%, two steps); (e) λ_{254}, $P(OMe)_3$, MeCN (for **130** and **131**: 67%); (f) (1) NH_3, MeOH; (2) Bu_4NF, THF; (3) Ac_2O, DMAP, MECN (69%, three steps); (g) Me_3SiCl, NaI, MECN (62%); (h) Et_3N, MeOH (47%).

Table 1
Synthesis of cyclonucleosides **140**–**144**, starting from the corresponding thiophenyl ethers **135**–**139**

Entry	Starting material	Cyclonucleoside	Yield (%)	Ref.
1	 **135**	 **140**	60	17
2	 **136**	 **141**	40	17
3	 **137**	 **142**	37	30
4	 **138**	 **143**	34	31
5	 **139**	 **144**	57	31

Chatgilialoglu et al.[35–37] reported the synthesis of 5′,8-*cyclo*-2′-deoxyinosine via both steady-state photolysis and continuous radiolysis. Starting from the 8-bromo-2′-deoxyinosine (**166**), irradiation with UV light at 254 nm in the presence of iodide ion in water afforded a mixture of the two cyclic diastereoisomers **167** and **168** in 38 and 10% yield. Irradiation of nucleoside **166** in the presence of $K_4[Fe(CN)_6]$ in water and *tert*-butanol gave the cyclonucleoside **167** as the major product in 64% yield (Scheme 27).

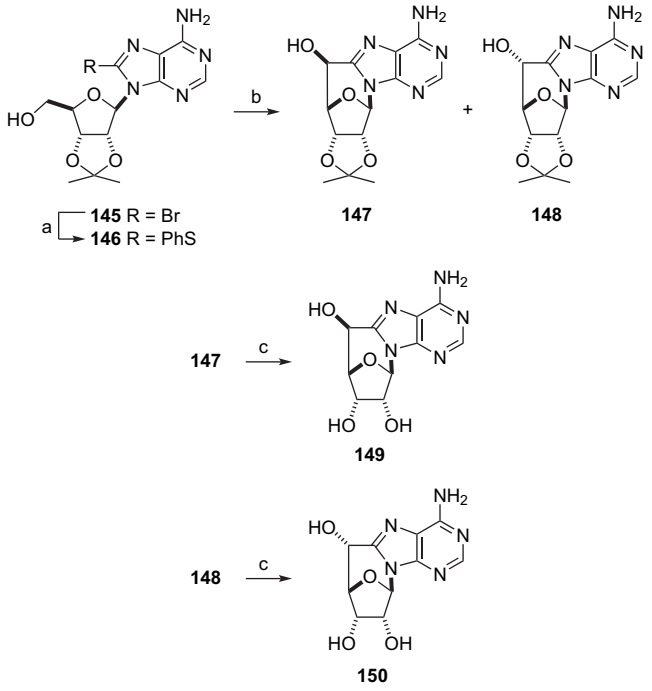
Quiclet-Sire et al.[38] reported the synthesis of cyclonucleosides via an aryltelluride exchange process. Starting from the mesylate **169**, reaction with anisyltelluride anion gave the anisyl derivative **170** in 86% yield. The radical cyclisation was effected by photolysis in the presence of the acetyl derivative of *N*-hydroxy-2-thiopyridone **172** to furnish the cyclonucleoside **171** in 60% yield. Classical deprotection yielded the target nucleoside **114** in 90% yield (Scheme 28).

The authors proposed the following mechanism for the cyclisation step.[38] The acetyl derivative of *N*-hydroxy-2-thiopyridone **172** was a convenient source of methyl radicals, via a Barton decarboxylation, which reacted with the anisyltelluride **170** to afford anisylmethyltelluride and the desired radical **173**. Radical cyclisation afforded the radical **174**, which was trapped by reaction with the thiocarbonyl group of **172** to give reformation of the methyl radical and the cyclonucleoside **175**, producing the target compound **114** by elimination of 2-thiopyridone (Scheme 29).

Radical 5-*exo*-*trig* cyclisations were applied for the preparation of cyclonucleosides. Tanaka et al. reported the synthesis of the 6,1′-cyclonucleosides **182** and **183** starting from the 2,2-dibromovinyl derivative **178**.[39,40] Introduction of the bromovinyl group onto compound **176** was carried on by reacting the 6-formyl derivative **177** with Ph_3PCBr_2 in 54% yield. Treatment of compound **178** with Bu_3SnH in the presence of AIBN in benzene furnished a mixture of the three cyclonucleosides **179**–**18** in 35, 6 and 7% yield, respectively. Classical deprotection of compounds **179** and **180** gave the target cyclonucleosides **182** and **183** in 84 and 89% yield, respectively (Scheme 30). The authors proposed that compounds **179** and **180** were obtained via a 5-*exo*-*trig* cyclisation and compound **181** via a 6-*endo* cyclisation. It was noteworthy that variations of the amount of hydride and photochemically induced radical reaction gave no improvement, either in terms of the total yield or the ratio of 5-*exo*/6-*endo* cyclisation.

Tanaka et al. proposed a radical 5-*exo*-*trig* cyclisation for the synthesis of the cyclonucleosides **179**–**183**.[40] For example, in the synthesis of the cyclonucleoside **179**, radical bromine abstraction from compound **178** by a stannyl radical furnished the vinyl radical intermediate **184** and then, after 5-*exo*-*trig* cyclisation, the radical **185**. From radical **185**, the hydrogen atom abstraction from Bu_3SnH afforded the target cyclonucleoside **179** (Scheme 31).

Tanaka et al. described the synthesis of the 2′-deoxy-6,1′-ethenouridine (**186**) and 2′-deoxy-6,1′-ethanouridine (**187**) starting



Scheme 22. Reagents and conditions: (a) PhSH, MeONa, MeOH (85%); (b) 400-W high-pressure Hg lamp, $P(OMe)_3$, MeCN; (c) HCl, H_2O (for **149**: 82%; for **150**: 97%).

from the cyclonucleoside **179**.[40] Compound **179** was subjected to halogen/lithium exchange followed by quenching with AcOH to furnish the alkene **184** in 52% yield. Selective hydrogenation of the 7,8-double bond in compound **186** with Rh/Al as a catalyst and subsequent deprotection of **187** gave the compound **188** in 89% yield (two steps). Classical desilylation of the glycone part of the compound **186** furnished the cyclonucleoside **189** in 83% yield (Scheme 32).

Application of this strategy permitted the synthesis of the cyclonucleosides **197**–**203**, starting from the dibromovinyl derivatives **190**–**196** (Table 2).[41]

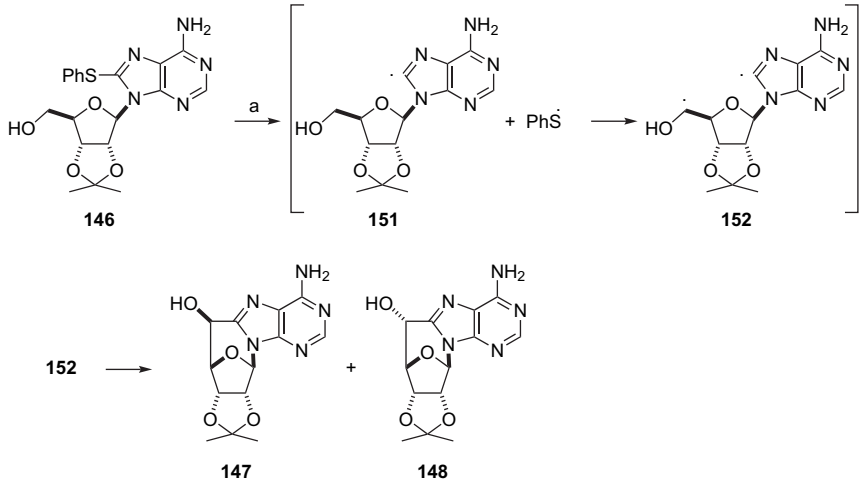
After various different propositions, Tanaka et al.[41,42] and Chatgilialoglu et al.[43] proposed a plausible 1,5-translocation mechanism for the synthesis of the anomeric spiro nucleosides **179**–**189** and **197**–**203**. As exemplified for the synthesis of cyclonucleoside **197**, bromine abstraction from the dibromovinyl derivative **190** by a stannyl radical generated the vinyl radical intermediate **204**, which, after 1,5-radical translocation to the anomeric position, furnished the radical **205**. Next, a rare 5-*endo*-*trig* cyclisation of the anomeric radical **205** afforded the radical **206**. A subsequent bromine atom ejection of compound **206** furnished the target cyclonucleoside **197** (Scheme 33).

2.2. *trans*-N-glycosidation

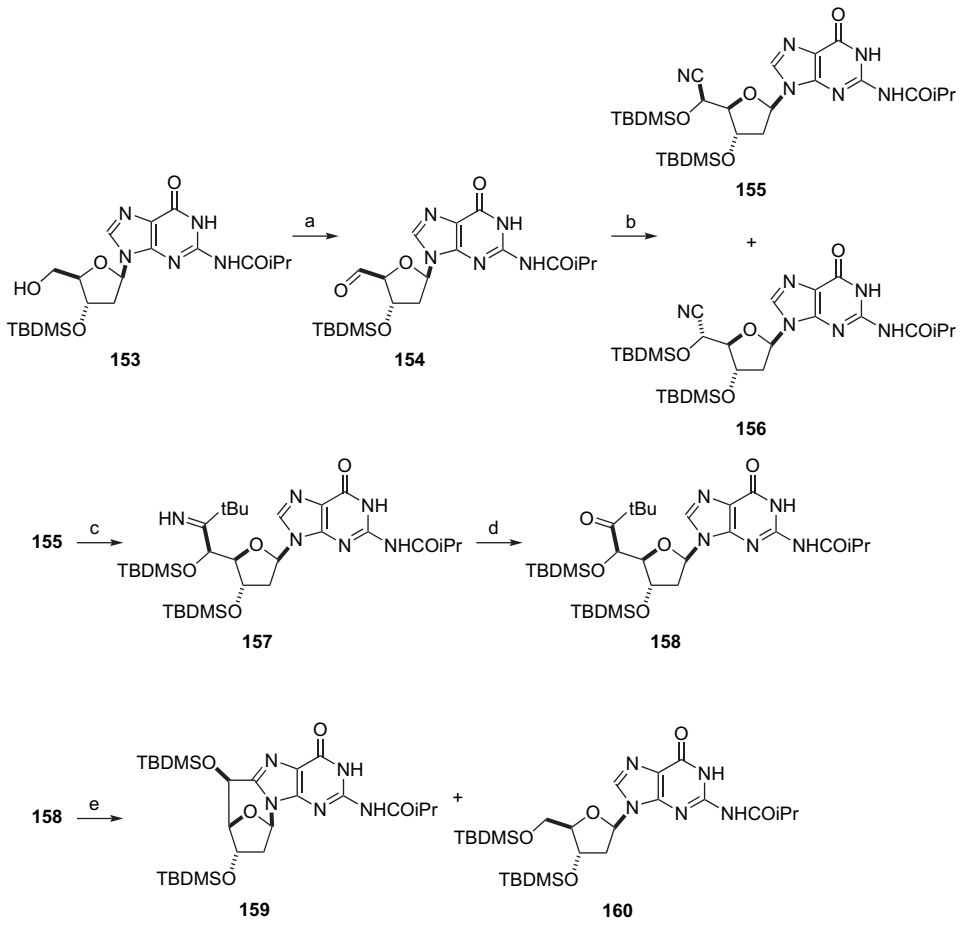
Different research groups have reported the synthesis of cyclonucleosides via either condensation of an ulose derivative and a (pyrimidinyl)methyllithium or condensation of the glycone moiety and the nucleobase via Sonogashira chemistry followed by intramolecular glycosidation. Ueda et al.[44] described the synthesis of 6,3′-methanouridine **212** and the analogue **213**, starting from the pentulofuranose **207**. Treatment of the ketone **207** with (2,4-dimethoxypyrimidin-6-yl)methyllithium, prepared from 2,4-dimethoxy-6-methylpyrimidine and BuLi, afforded diastereoselectively the corresponding alcohol **208** having the *R* absolute configuration for the carbon atom in the 3′-position. After removal of the silyl group and subsequent benzoylation, the benzoate **209** was converted into the diacetates **210** in 92% yield. Treatment of compound **210** with $SnCl_4$ and then classical deprotection furnished the target cyclonucleoside **212** in 43% yield (two steps) (Scheme 34). Classical treatment of the cyclonucleoside **211** with methanolic ammonia afforded the corresponding cytidine analogue **213** in 62% yield (Scheme 34).

The authors reported in the same paper the formation of the corresponding 2′-deoxy analogues **218** and **219**, starting from the cyclonucleoside **211**.[44] Treatment of compound **211** with 2,3-dihydrofuran in the presence of PTSA in dioxane afforded the tetrahydrofuranyl derivative **214** in 82% yield. After selective 2′-*O*-deacetylation of compound **214** and then imidazolylthiocarbonylation of compound **215**, the ester derivative **216** was submitted to Barton–McCombie radical deoxygenation by treatment with Bu_3SnH and AIBN to give the 2′-deoxy nucleoside **217** in 42% yield (three steps). Classical alkaline hydrolysis or treatment with methanolic ammonia of compound **217** afforded the target cyclonucleosides **218** and **219** in 91% yield in both cases (Scheme 35).

Application of this strategy was described by the same authors to furnish the cyclonucleoside **70** and the analogue **225**.[45] Starting from the aldehyde **220**, addition of (2,4-dimethoxypyrimidin-6-yl)methyllithium yielded a diastereoisomeric mixture of alcohol **221** in 65% yield. To prevent dehydration during the intramolecular glycosidation conversion of the alcohol **221** into the corresponding alkane **222** was carried on via the 5-imidazolylthiocarbonate. Next,



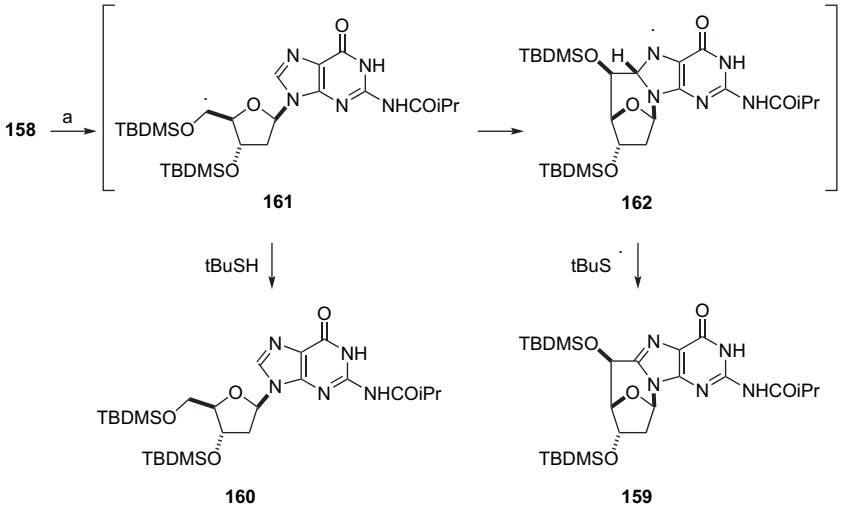
Scheme 23. Reagents and conditions: (a) 400-W high-pressure Hg lamp, $P(OMe)_3$, MeCN.



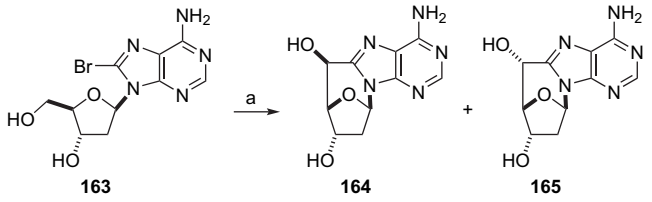
Scheme 24. Reagents and conditions: (a) EDC, pyr, CF_3COOH, toluene, DMSO (95%); (b) TMSCN, ZnI_2, CH_2Cl_2 (88%) then TBDMSCl, imidazole, DMF (25%); (c) *t*-BuLi, THF (32%); (d) MeCOOH, THF, H_2O (78%); (e) 1000-W Xe lamp, *t*-BuSH, THF (for **159**: 20%; for **160**: 27%).

acidic hydrolysis of compound **222** and subsequent acetylation afforded the triacetate **223** in 72% yield (two steps). Treatment of compound **223** with $SnCl_4$ and aqueous sodium hydroxide in dioxane furnished the target cyclonucleoside **70** in 44% yield (two steps) (Scheme 36). Compound **224** in methanolic ammonia afforded the cytidine analogue **225** in 94% yield.

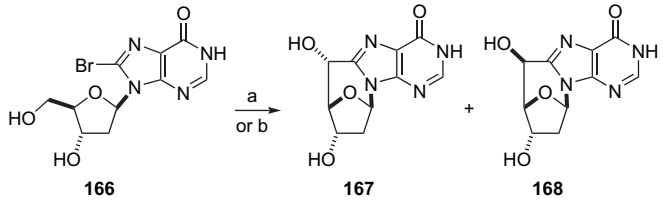
An alternative synthesis of 6,6′-cyclonucleosides was developed by the same authors[45] using a Peterson reaction followed by hydrogenation of the olefinic bond. Conversion of 2,4-dimethoxy-6-methylpyrimidine into the corresponding 6-trimethylsilyl derivative and condensation with the aldehyde **220** in the presence of LDA and $CeCl_3$ afforded a mixture of the olefin **227** and silanol **226**. Without separation, elimination of the silanol **226** was promoted by acetylation of the hydroxyl group by treatment with AcCl and diisopropylethylamine followed by treatment with TBAF to furnish the olefin **227** as an *E* and *Z* mixture. Classical hydrogenation of the alkene **227** gave the acetal **222** in 86% yield. The authors noted that this approach is superior to that described in Scheme 36 in that it



Scheme 25. Reagents and conditions: (a) 1000-W Xe lamp, *t*-BuSH, THF.



Scheme 26. Reagents and conditions: (a) λ_{254}, NaI, H_2O (for **164**: 41%; for **165**: 24%).

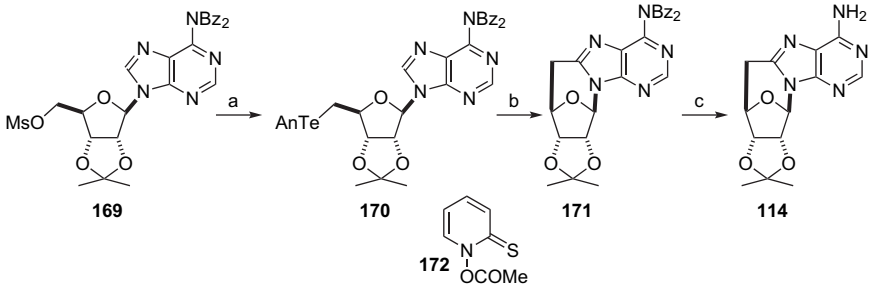


Scheme 27. Reagents and conditions: (a) λ_{254}, NaI, H_2O (for **167**: 38%; for **168**: 10%); (b) $K_4[Fe(CN)_6]$, H_2O, *t*-BuOH (for **167**: 64%, based on recovered starting material).

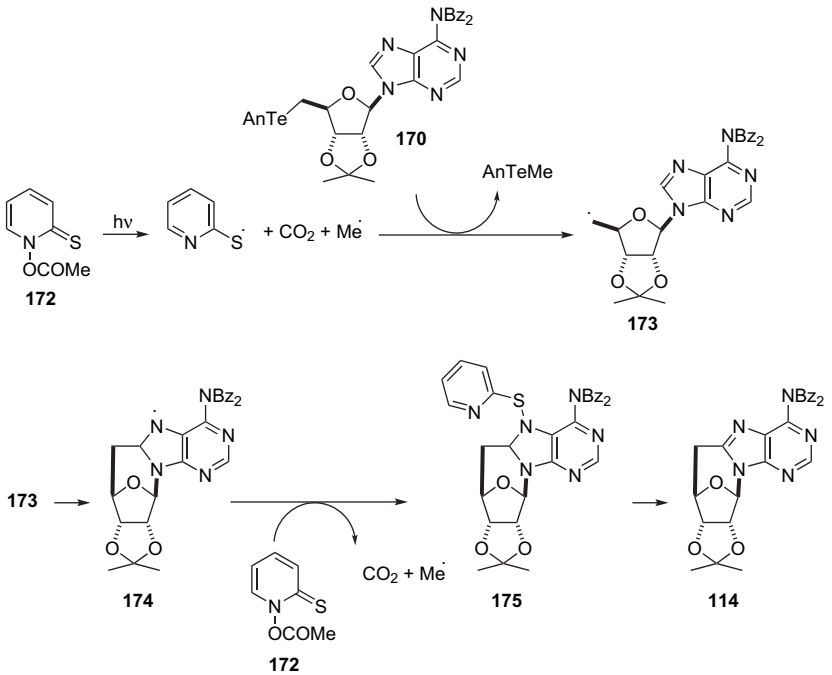
eliminates a somewhat laborious separation of tributyltin compounds formed in the deoxygenation step (Scheme 37).

Ueda et al. applied the same strategy for the synthesis of 6,2′-cyclonucleosides **234** and **235**.[46] Starting from isopropyl β-D-*erythro*-2-pentulofuranoside **228**, condensation with 2,4-dimethoxy-6-trimethylsilylmethylpyrimidine in the presence of *n*-BuLi afforded the nucleoside analogue **229** having the *Z* configuration via a Peterson olefination. Catalytic hydrogenation of the alkene **229** gave the 2-*C*-pyrimidinylmethyl-*arabino*-furanoside **230** in 82% yield. The hydrogenation from the α-side of the sugar ring was due to the steric hindrance of the bulkier protecting group in the 1-β-position. After deprotection of the silylated diol **230**, protection with Bz_2O and then acetylation of the anomeric position of compound **231**, the anomeric mixture of 3′,5′-di-*O*-benzoate **232** was subjected to an intramolecular glycosidation with $SnCl_4$, giving only the diastereoisomer **233** in 39% yield (five steps). Treatment of compound **233** with NaOH in aqueous dioxane and with methanolic ammonia furnished the corresponding uridine and cytidine analogues **234** and **235**, respectively, in 81 and 70% yield (Scheme 38).

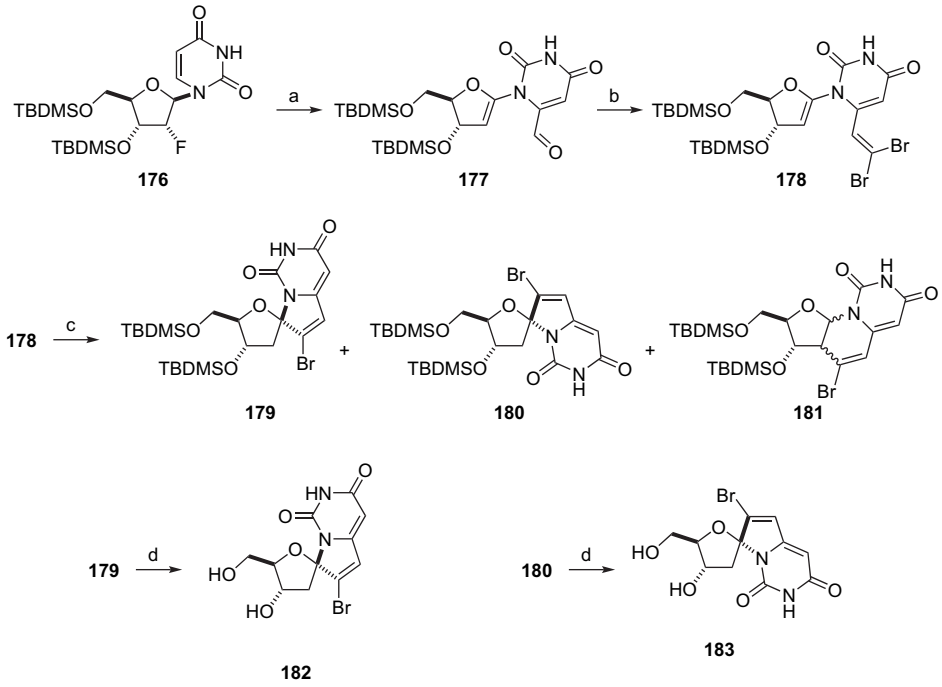
De Mesmaeker et al. reported a route to the 6,3′-cyclonucleosides, which employed the key steps of a Sonogashira reaction and an intramolecular glycosidation.[47] Starting from the ulose **207**, addition of 2-trimethylsilylethynyllithium on the β-side of the glycone and desilylation afforded the diol **236** in 96% yield. After protection of the diol **236** with 2,4-dichlorobenzyl chloride, the protected D-ribose analogue **237** was subjected to a palladium-catalysed cross-coupling with 2,4-dimethoxy-6-iodopyrimidine to give the alkyne **238** in 89% yield. Hydrogenation of compound **238**



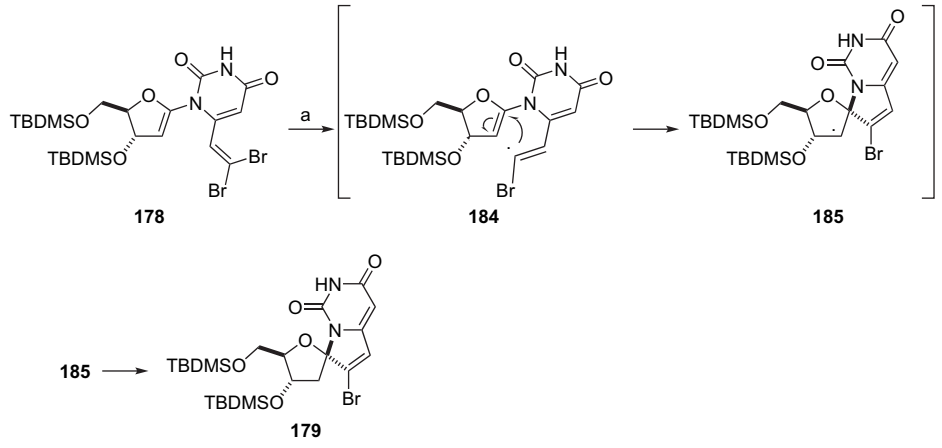
Scheme 28. Reagents and conditions: (a) $(AnTe)_2$, $NaBH_4$, EtOH, THF (86%); (b) **162**, CH_2Cl_2, *hν* (60%); (c) NH_3, MeOH (90%).



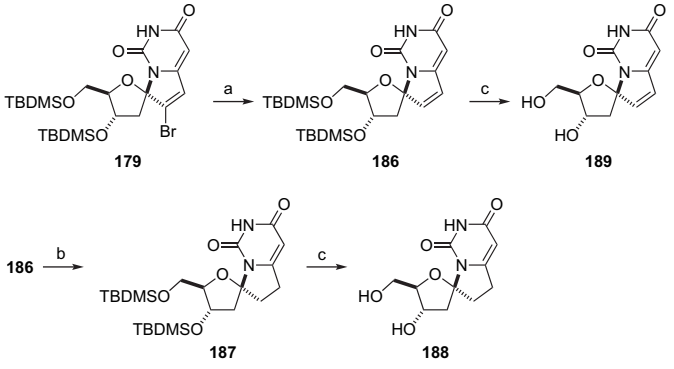
Scheme 29. Mechanism of the aryltelluride exchange process.



Scheme 30. Reagents and conditions: (a) (1) LDA, THF; (2) HCOOMe; (b) Ph_3PCBr_2, CH_2Cl_2, DMF (54%); (c) Bu_3SnH, AIBN, benzene (for **179**: 35%; for **180**: 6%; for **181**: 7%); (d) TBAF, AcOH, THF (for **182**: 84%; for **183**: 89%).



Scheme 31. Reagents and conditions: (a) Bu_3SnH, AIBN, benzene.



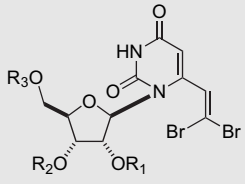
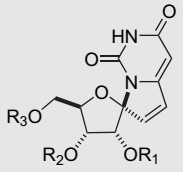
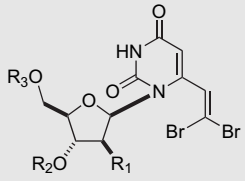
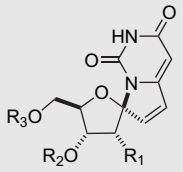
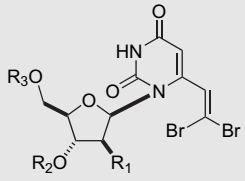
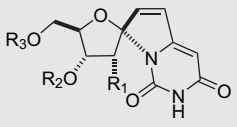
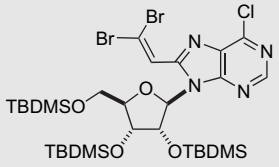
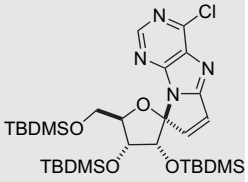
Scheme 32. Reagents and conditions: (a) BuLi, THF, then AcOH (52%); (b) Et_3N, 5% Rh/Al, MeOH (95%); (c) TBAF, AcOH, THF (for **188**: 94%; for **189**: 83%).

in the presence of Raney Ni followed by acidic hydrolysis of compound **239** and subsequent acetylation afforded the diacetates **240** in 75% yield (two steps). Intramolecular glycosidation using $SnCl_4$ and deprotection of the 2′-hydroxyl group in **241** afforded the nucleoside analogue **242** in 80% yield (two steps). Protection of the acidic nitrogen atom N-3 with a BOM group in the presence of DBU and methylation of the secondary hydroxyl group of **243** with methyl iodide in the presence of Ag_2O, followed by selective hydrogenolysis of **244**, furnished the target cyclonucleoside **245** in 42% yield (three steps) (Scheme 39).

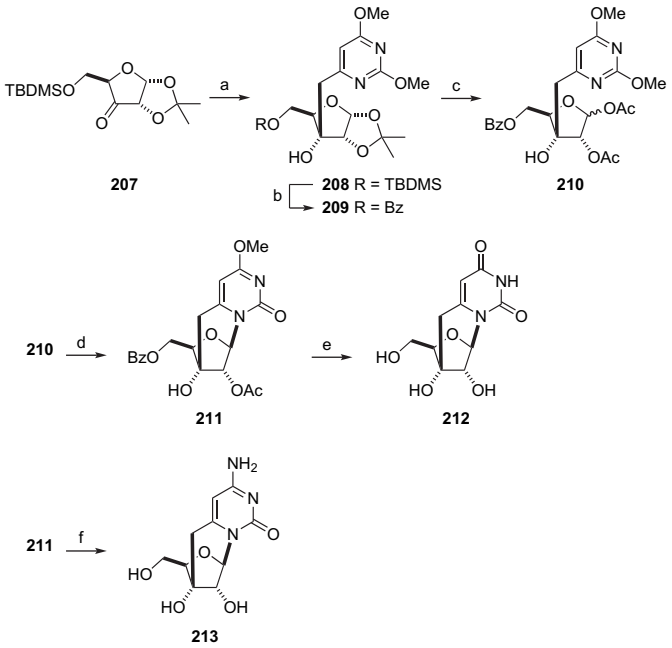
2.3. Substitution

The lithiation chemistry of uridine derivatives was developed by Miyasaka et al.[48] Recently, Yoshimura et al. have reported an efficient intramolecular alkylation of 5′-deoxy-5′-iodouridine to furnish the 6,5′-*C*-cyclonucleoside via lithiation at the 6-position of uridine.[49] Starting from 5′-deoxy-5′-iodouridine derivative **246**,

Table 2
Synthesis of cyclonucleosides **197**–**203** starting from the corresponding β,β-dibromovinyl nucleosides **190**–**196**[41]

Entry		Starting material		Major cyclonucleoside
				
1	**190**	R_1R_2=C(Me)$_2$; R_3=TBDMS	**197**	40%
2	**191**	R_1=R_2=R_3=TBDMS	**198**	50%
3	**192**	R_1=R_2=R_3=Ac	**199**	40%
				
4	**193**	R_1=H; R_2R_3=TIPDS	**200**	23%
				
5	**194**	R_1=OAc; R_2=R_3=Ac	**201**	21%
6	**195**	R_1=OH; R_2=R_3=TBDMS	**202**	26%
				
7	**196**	R_1=R_2=R_3=TBDMS	**203**	18%

treatment with LiHMDS in the presence of Ph_2SiCl_2 gave the 6,5′-*C*-cyclonucleoside **5** in 88% yield and a trace of the 6-silyl derivative **247**. The use of TMSCl or $MePh_2SiCl$ enhanced the yield of the 6-silyl

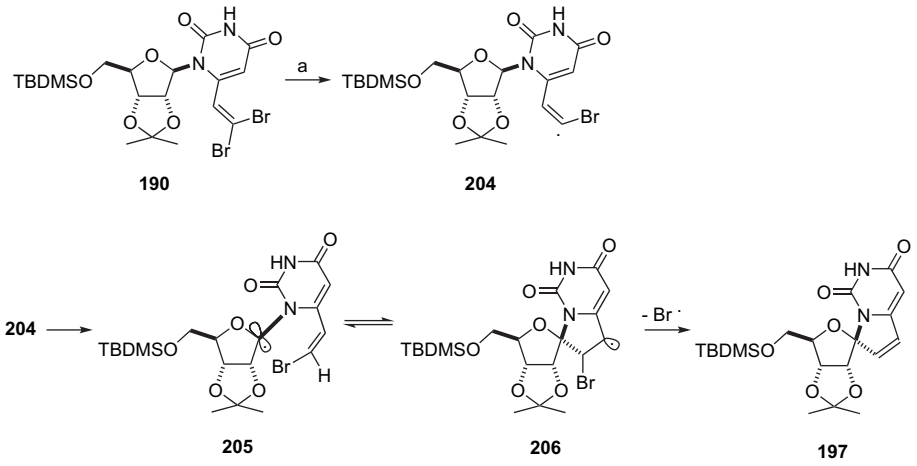


Scheme 34. Reagents and conditions: (a) (2,4-dimethoxypyrimidin-6-yl)methyllithium, THF (75%); (b) (1) TBAF, THF; (2) BzCl, pyr (91%); (c) CF_3COOH, H_2O, then Ac_2O, CH_2Cl_2, Et_3N (92%); (d) $SnCl_4$, MeCN (82%); (e) NaOH, H_2O, dioxane (53%); (f) NH_3, MeOH (62%).

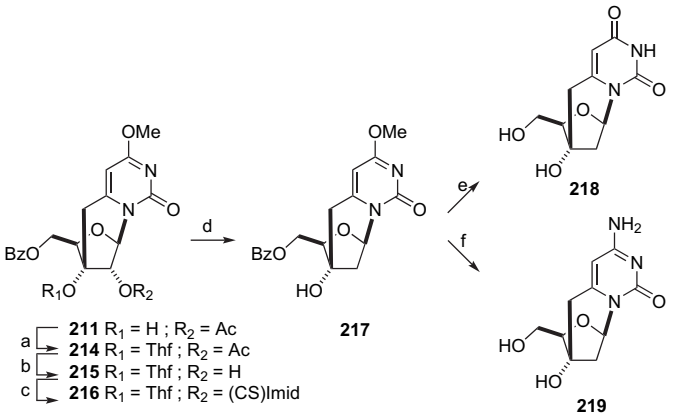
nucleoside **247**. It is notable that the use of LDA having a higher basicity gave a complex mixture of products, from which **5** was isolated only in 8% yield and the use of simple LiHMDS gave none of the desired cyclonucleoside **5** (Scheme 40).

Yoshimura et al.[49] explained that the LiHMDS combined silylating agent led to the compound **248** by silylation of the O-4 of the uracil moiety. Due to the loss of the negative charge on the N-3 position, LiHMDS was able to generate the C-6 lithio derivative **249**, which gave the cyclonucleoside **5** (Scheme 41).

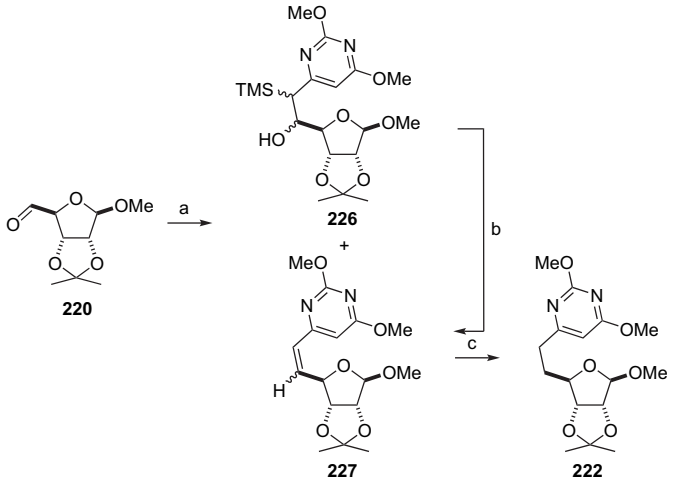
Ueda et al.[50] described the synthesis of novel cyclonucleosides having a methylene link via the sodium salt of a dialkyl malonate. Treatment of 8-bromo-2′-*O*-tosyladenosine (**250**), obtained in five steps from adenosine, with NaSMe afforded the thioether **251** in 90% yield. Acetylation of **251** and subsequent oxidation with a finely powdered $KMnO_4$ gave the 8-methanesulfonyl derivative **252** in 90% yield (two steps). Nucleoside **252** was treated with the sodium salt of diethyl malonate in tetrahydrofuran at reflux to afford the



Scheme 33. Reagents and conditions: (a) Bu_3SnH, AIBN, benzene.



Scheme 35. Reagents and conditions: (a) 2,3-dihydrofuran, PTSA, dioxane (82%); (b) Et_3N, MeOH (80%); (c) $(CS)Imid_2$, DMF (72%); (d) Bu_3SnH, AIBN, toluene (73%); (e) NaOH 2 N, dioxane (91%); (f) NH_3, MeOH (91%).



Scheme 37. Reagents and conditions: (a) 2,4-dimethoxy-6-trimethylsilylmethylpyrimidine, LDA, $CeCl_3$, THF; (b) (1) AcCl, *i*-Pr_2EtN, CH_2Cl_2; (2) TBAF, THF (74%); (c) H_2, Pd/C, AcOEt (86%).

desired cyclonucleoside **253** in 79% yield. Decarboxylation of the ester **253** by heating under reflux in aqueous pyridine followed by deacetylation with ammonia gave the target cyclonucleoside **254** in 65% yield (Scheme 42).

Application of this strategy was described by the authors for the synthesis of the cyclonucleoside **255** (Fig. 6).[51]

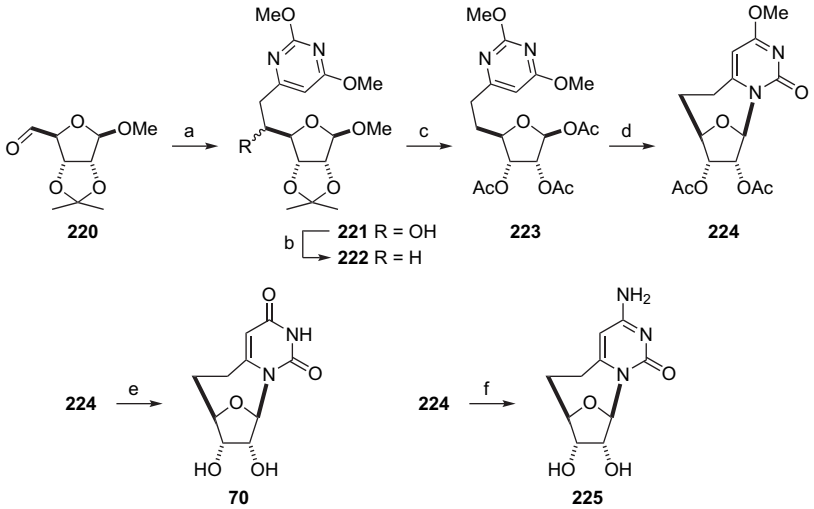
Ueda et al.[52] described the synthesis of 2′-deoxy-6,2′-methanocyclouridine (**234**) via the 2′(*S*)-ethoxycarbonylmethyl derivative **31**. After bromination of the nucleobase, treatment of compound **256** with DBU in refluxing dioxane afforded the expected nucleoside **257** by a Michael addition of the generated 2″-carbanion to C-6 of the base portion followed by dehydrobromination in 65% yield. Heating of compound **257** in DMSO in the presence of H_2O and NaCl at 140 °C resulted in de-ethoxycarbonylation to afford the 6,2′-methano derivative **258** in 32% yield. Subsequent deprotection of the two hydroxyl groups gave the target nucleoside **234** in 71% yield (Scheme 43).

2.4. Addition

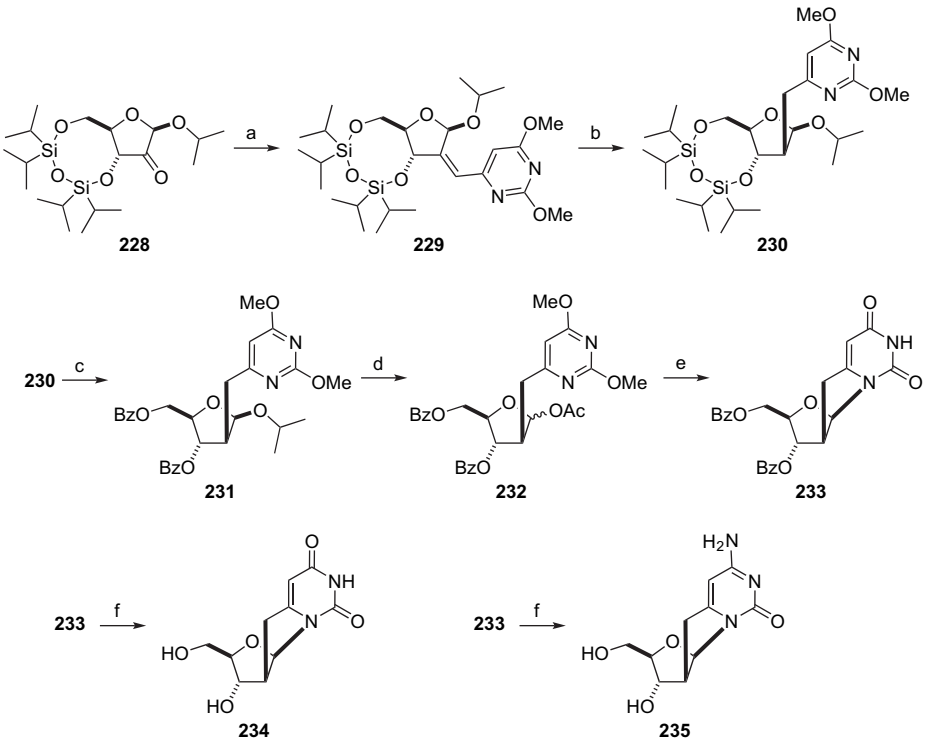
Otter et al. reported the intramolecular aldol reaction as an effective method to afford the corresponding cyclonucleoside.[53] Starting from 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**259**), oxidation with DMSO and DCC in the presence of pyridinium trifluoroacetate gave the 5′-aldehyde **260**. Next, treatment of compound **260** with NaOH generated compound **261** and permitted the diastereoselective hydroxyalkylation to afford the cyclonucleoside **262** having the 5′-*S* absolute configuration in 44% yield (two steps). The removal of the pyrimidine 5-hydroxyl group of **262** was realised by mesylation and subsequent hydrogenation of the mesylate **263** in 43% yield (two steps). Hydrolysis of compound **264** in acetic acid afforded the desired 6,5′-cyclouridine (**265**) in 57% yield (Scheme 44).

Fox et al.[54] have described another strategy using the corresponding 5′-imidazolidine derivative **266**. Oxidation of the nucleoside **259** and subsequent protection of the aldehyde with *N*,*N*′-diphenylethylenediamine afforded the 1,3-diphenylimidazolidine **266** in 71% yield (two steps). Treatment of compound **266** with ethanolic ammonia and with Dowex 50 H+ in THF and H_2O led to the deacetylated compound **267** and then, with $NaHCO_3$, afforded the cyclonucleoside **262** in 82% yield via the aldehyde intermediate **261** (Scheme 45).

The authors[54] suggested that the remarkable stereoselectivity may be explained by the dihedral angle $O_{4'}$–$C_{4'}$–$C_{5'}$–$O_{5'}$, which permitted the attack of the C-6 anion on the 5′-aldehyde, giving the *S* absolute configuration. Fox et al. explained that the formation of



Scheme 36. Reagents and conditions: (a) (2,4-dimethoxypyrimidin-6-yl)methyllithium, THF (65%); (b) (1) $(CS)Imid_2$, DMF; (2) Bu_3SnH, AIBN, toluene (70%); (c) (1) CF_3COOH, H_2O; (2) Ac_2O, CH_2Cl_2, $N(Et)_3$ (72%); (d) $SnCl_4$, MeCN (66%); (e) NaOH 2 N, dioxane (66%); (f) NH_3, MeOH (94%).

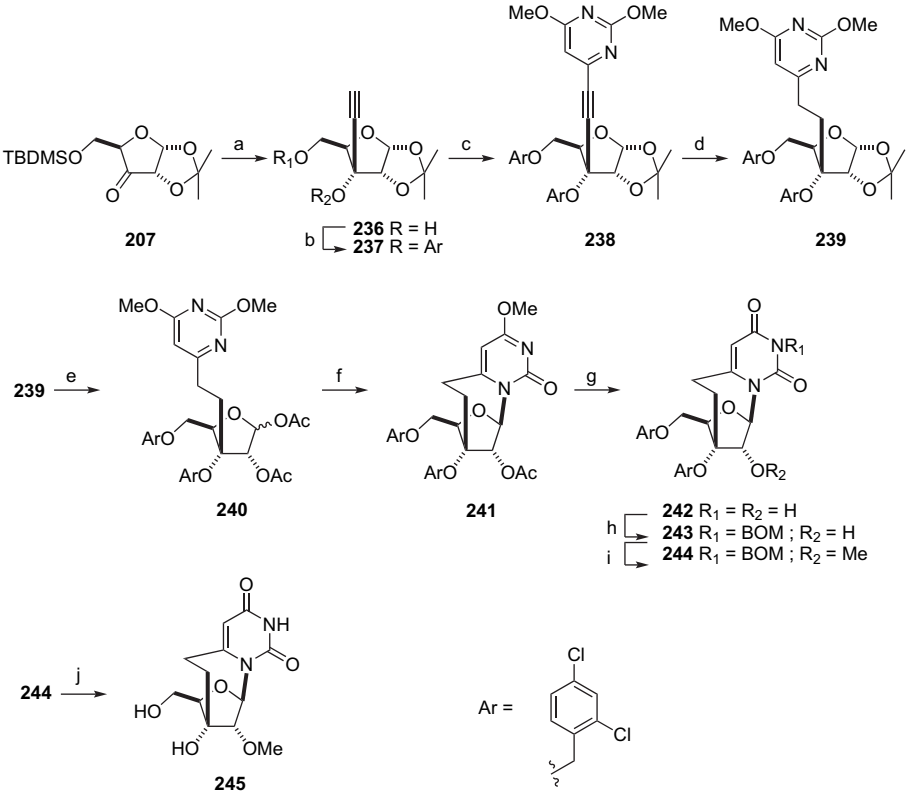


Scheme 38. Reagents and conditions: (a) BuLi, 2,4-dimethoxy-6-trimethylsilylmethylpyrimidine, THF (76%); (b) H_2, Pd/C, AcOEt (82%); (c) (1) TBAF, THF; (2) Bz_2O, DMAP, Et_3N, MeCN (88%); (d) (1) CF_3COOH; (2) Ac_2O, DMAP, pyr (57%); (e) $SnCl_4$, MeCN (78%); (f) NaOH 2 N, dioxane (81%); (g) NH_3, MeOH (70%).

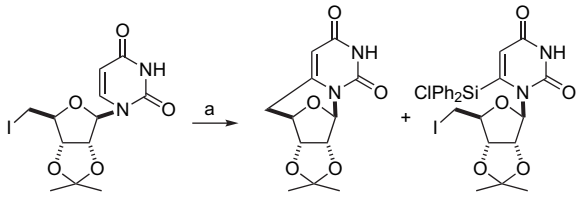
the cyclonucleoside **262** proceeded through the formation of the mesomeric anion **268** and nucleophilic attack of the C-6 anion **269** on the 5′-carbonyl group yielding the intermediate **270**, which could tautomerise to give the cyclonucleoside **262** (Scheme 46).

3. Conclusions

A major initiative to synthesise cyclonucleosides has been led by attempts to discover compounds with increased activity over



Scheme 39. Reagents and conditions: (a) (1) TMSCCLi, THF; (2) TBAF, AcOH, THF (96%); (b) 2,4-dichlorobenzyl chloride, Bu_4NI, NaH, DMF (79%); (c) 2,4-dimethoxy-6-iodopyrimidine, $PdCl_2(PPh_3)_2$, CuI, 2,2,6,6-tetramethylpiperidine (89%); (d) H_2, Ni/Ra, MeOH, THF (94%); (e) (1) CF_3COOH, H_2O; (2) Ac_2O, pyr (80%); (f) $SnCl_4$, CH_2Cl_2 (82%); (g) NaOH 2 N, dioxane (97%); (h) BOMCl, DBU, DMF (79%); (i) MeI, Ag_2O (91%); (j) (1) H_2, Pd/C 5%, THF; (2) H_2, Pd/C 5%, AcONa, MeOH; (3) H_2, Pd/C 10% MeOH (58%).



Scheme 40. Reagents and conditions: (a) Ph_2SiCl_2, LiHMDS, THF (for **5**: 88%).

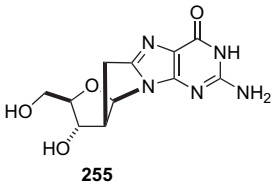
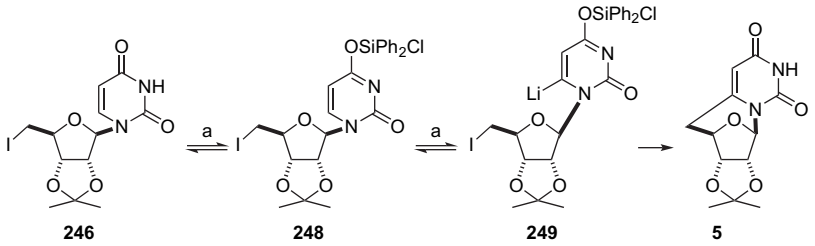
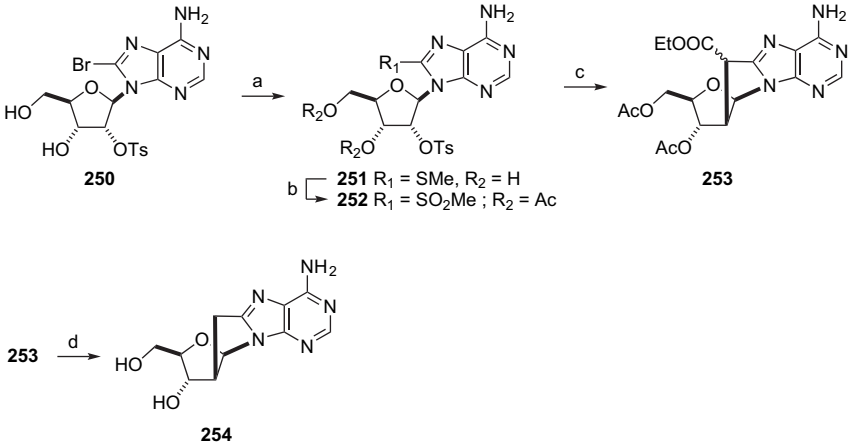


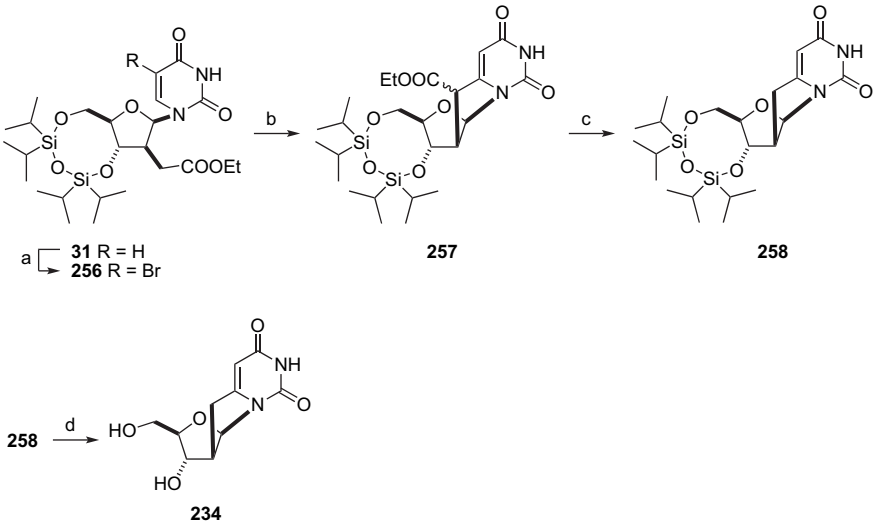
Figure 6. Cyclonucleoside **255**.



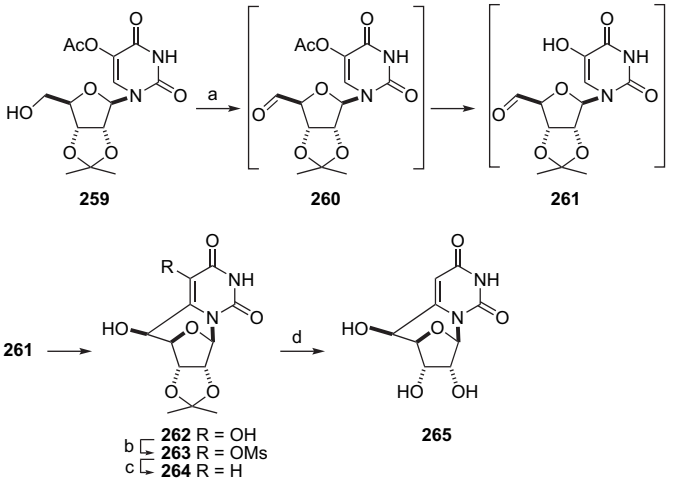
Scheme 41. Reagents and conditions: (a) Ph_2SiCl_2, LiHMDS, THF.



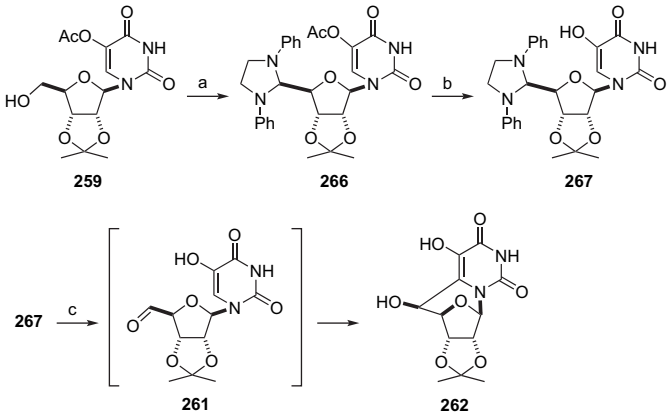
Scheme 42. Reagents and conditions: (a) 15% aq NaSMe, DMF (90%); (b) (1) Ac_2O, pyr; (2) 70% aq AcOH, $KMnO_4$ (90%); (c) $CH_2(COOEt)_2$, NaH, THF (79%); (d) 85% aq Pyr, then NH_3, H_2O (65%).



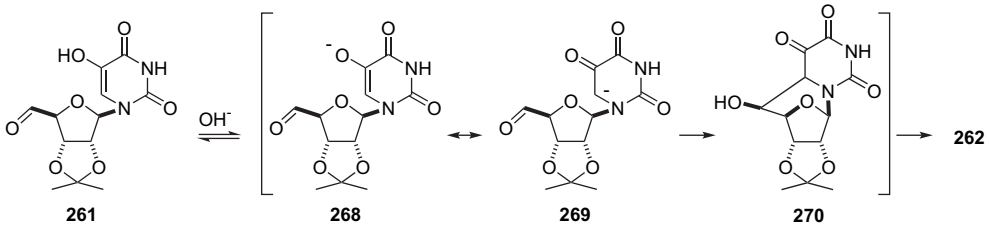
Scheme 43. Reagents and conditions: (a) AcOH, AcONa, Br_2 (73%); (b) DBU, dioxane (65%); (c) H_2O, NaCl, DMSO (32%); (d) TBAF, THF (71%).



Scheme 44. Reagents and conditions: (a) (1) DCC, CF_3COOH, pyr, DMSO; (2) NaOH 1 N, MeOH (44%); (b) MsCl, benzene, pyr (75%); (c) Pd/C, H_2O, Et_3N, MeOH (57%); (d) AcOH, H_2O (87%).



Scheme 45. Reagents and conditions: (a) (1) DCC, CF_3COOH, pyr, DMSO; (2) 1,2-diphenylethylenediamine, CH_2Cl_2 (71%); (b) NH_3, EtOH (95%); (c) Dowex 50 H^+, THF, H_2O, then $NaHCO_3$ (82%).



Scheme 46. Mechanism for the stereoselective synthesis of the cyclonucleoside **262**.

natural nucleos(t)ides or nucleos(t)ide analogues to provide structure–activity data. To date, the majority of work has been directed towards cyclonucleosides having a linker: (i) at either the 6,5′-, 6,3′-, 6,2′-, or 6,1′-position in the field of pyrimidine nucleosides; and (ii) at either the 8,5′-, 8,3′-, 8,2′-, or 8,1′-position in the field of purine nucleosides. Most of the strategies employed to obtain cyclonucleosides were convergent approaches, starting from nucleosides (radical reaction, substitution, addition) or starting from carbohydrates (*trans*-N-glycosidation). Radical reactions have been used by the generation of a radical employing chemical and photochemical initiation. In the first case, the formation of a radical at a position of the glycone moiety and intramolecular radical addition at a carbon atom of the nucleobase were described.[9–25] In the second case, the formation of a radical at either a position of the glycone moiety or the nucleobase followed by intramolecular radical addition was developed.[26–43] Substitution approaches have been used by the application of lithiation chemistry[48,49] or malonate strategy.[50–52] In the case of metallation, lithiation at the 6-position of uridine was effected and intramolecular cyclisation with a carbon atom of the glycone moiety was reported.[48,49] In the case of the malonate strategy, two approaches were described: (i) addition of diethyl malonate to nucleoside analogue having two leaving groups;[50,51] and (ii) formation of nucleoside analogues having an ethoxycarbonylmethyl group.[52] Intramolecular aldol reactions have been used to a lesser extent in which the cyclisation is generated between the nucleobase and a formyl group in the 5′-position.[53,54] *trans*-N-glycosidation has included those reactions in which the nucleobase was condensed with the glycone moiety in the 5′-, 3′- or 2′-position via lithiation chemistry[44–46] or Sonogashira methodology.[47]

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Biographical sketch

Christophe Len was born in L'Isle Adam (France) in 1966. He received his Ph.D. from the University of Picardie-Jules Verne (UPJV) in Amiens (France) under the supervision of Professor P. Villa in the field of carbohydrate chemistry. In 1996, he joined Doctor G. Mackenzie's group at the University of Hull (UK) as a post-doctoral fellow to work on the synthesis of nucleoside analogues. In 1997, he became Maître de Conférences at UPJV and worked on the chemistry of antiviral nucleoside analogues specialising on those with novel glycone systems. In 2003, he received his habilitation and was promoted to full Professor in 2004 at the University of Poitiers (France). His current main research interests are in the total synthesis of natural products and bioactive molecules, which include carbohydrates and nucleoside analogues having restricted conformations.

Martine Mondon was born in 1949 in Talence (France). She received her 'doctorat de 3ème cycle' from the University of Paris VI under the direction of Dr Claude Wakselman (1973) for her work on the chemistry of lithium dialkylcuprates, and her Ph.D. from the University of Sherbrooke (Canada) under the direction of Professor Jean Lessard (1977) for her work on radical and photochemical addition of *N*-haloamides to olefins. She entered the Centre National de la Recherche Scientifique (CNRS) in 1978 and joined the group of Professor Jean-Pierre Gesson in Poitiers (France) to develop the synthesis, transformation and reactivity of natural products. In 2004, she worked in Professor Christophe Len's group in the field of nucleoside analogues having restricted conformations.

Jacques Lebreton was born in Guérande (France) in 1960. He received his Ph.D. degree (1986) from the University of Paris XI-Orsay under the supervision of Professor Eric Brown (Le Mans). His thesis work included the total synthesis of C-nor D-homosteroids. In 1986, he started his first post-doctoral fellowship with Professor James A. Marshall at the University of South Carolina working on the [2,3]-Wittig rearrangement and its application in total synthesis. Following a second post-doctoral fellowship with Professor Robert E. Ireland at the University of Virginia working on the total synthesis of monensine, he joined in 1990 the laboratories of CIBA-GEIGY (Novartis) in Basle, where he worked in Dr. Alain De Mesmaeker's group in the field of antisens. In 1994, he joined the CNRS and spent a few years in the group of Dr. Jean Villiéras (UMR CNRS 6513, Nantes) concerned with organometallic chemistry. In 1998, he was promoted to Professor at the University of Nantes. His major research interests are organometallic chemistry and medicinal chemistry. In 2000 with his friend and colleague A. Guingant, he set up a research group, named Symbiose, devoted to developing research at the interface between chemistry and biology. Most of his recent work has focussed on the synthesis of bioactive molecules, such as steroids, nucleosides, alkaloids, macrolides and azasugars, for biological evaluation purposes in the fields of HIV, central nervous system diseases and cancer through academic and industrial collaborations. His research efforts also include the synthesis of labelled molecules to study biological processes.