Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 9085–9107

Tetrahedron report number 768

# Synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides having variations at either or both of the 2′- and 3′-positions

Christophe Len[a,*] and Grahame Mackenzie[b]

[a]*Synthèse et Réactivité des Substances Naturelles, UMR 6514 CNRS, Université de Poitiers, 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*
[b]*Department of Chemistry, University of Hull, Hull HU6 7RX, UK*

Received 10 July 2006
Available online 4 August 2006

**Contents**



## 1. Introduction

Several nucleoside analogues have been shown to be highly effective as antiviral and antitumour agents. 2′,3′-Dideoxynucleosides (ddNs) and 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns), namely the nucleoside reverse transcriptase inhibitors (NRTI), form the most important class of compounds active against the human immunodeficiency virus (HIV), which causes AIDS. The NRTI approved by the US Food and Drug Administration (US FDA) for the treatment of AIDS are 3′-azido-2′,3′-dideoxythymidine (AZT, zidovudine),[1–4] 2′,3′-dideoxycytidine (ddC, zalcitabine),[5,6]

*Abbreviations*: ABC, (1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol; Ac, acetyl; AD-mix, asymmetric dihydroxylation; AIBN, azobisisobutyronitrile(2,2′-azo(2-methylpropionitrile)); AIDS, acquired immunodeficiency syndrome; All, allyl; Ar, *p*-methoxyphenyl; AZT, 3′-azido-2′,3′-dideoxythymidine; bis(POC)PMPA, tenofovir disoproxil fumarate; Bn, benzyl; BSA, *N*,*O*-bis(trimethylsilyl)acetamide; Bz, benzoyl; Bu, butyl; DAST, (diethylamino)sulfur trifluoride; dba, dibenzylideneacetone; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DBU, diazadicycloundecane; ddI, 2′,3′-dideoxyinosine; ddNs, 2′,3′-dideoxynucleosides; DEAD, diethylazodicarboxylate; DIBALH, diisobutylaluminium hydride; DMF, *N*,*N*-dimethylformamide; d4Ns, 2′,3′-didehydro-2′,3′-dideoxynucleosides; d4T, 2′,3′-didehydro-2′,3′-dideoxythymidine; ddc, 2′,3′-dideoxycytidine; DMAP, 4-dimethylaminopyridine; DMSO, dimethylsulfoxide; DMTr, dimethoxytrityl; Et, ethyl; FTC, 5-fluoro-2′,3′-dideoxy-3′-thia-β-L-cytidine; HIV, human immunodeficiency virus; HMDS, 1,1,1,3,3,3-hexamethyldisilazane; HMPA, hexamethylphosphoramide; imid, imidazol-1-yl; LTMP, lithium 2,2,6,6-tetramethylpiperidide; MCPBA, *m*-chloroperoxybenzoic acid; Me, methyl; MMTr, monomethoxytrityl; Ms, mesyl; NBS, *N*-bromosuccinimide; NMO, *N*-methylmorpholine-*N*-oxide; NMR, nuclear magnetic resonance; NRTI, nucleoside reverse transcriptase inhibitors; PCC, pyridinium chlorochromate; Ph, phenyl; Piv, pivaloyl; PTSA, *p*-toluenesulfonic acid; SAR, structure–activity relationship; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; 3TC, 2′,3′-dideoxy-3′-thia-β-L-cytidine; TDS, *tert*-butyldiphenylsilyl; Tf, triflate; TFA, trifluoroacetic acid; TFMTMS, trifluoromethyltrimethylsilane; TIPDS, tetraisopropyldisiloxan-1,3-diyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMSOTf, trimethylsilyl triflluoromethanesulfonate; THF, tetrahydrofurane; Tr, trityl; Ts, tosyl; US FDA, US Food and Drug Administration.

* Corresponding author. Tel.: +33 5 49 36 63 89; fax: +33 5 49 45 37 02; e-mail: christophe.len@univ-poitiers.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.07.050

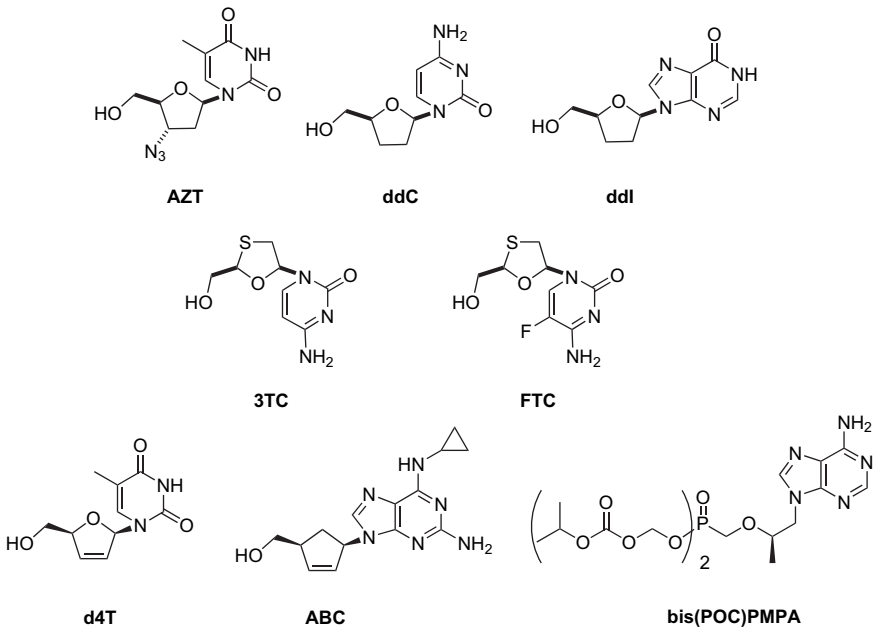



**Figure 1**. NRTI approved by the US FDA for the treatment of AIDS.

2′,3′-dideoxyinosine (ddI, didanosine),[7,8] 2′,3′-dideoxy-3′-thia-β-L-cytidine (3TC, lamivudine),[9,10] 5-fluoro-2′,3′-dideoxy-3′-thia-β-L-cytidine (FTC, emtricitabine),[11,12] 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, stavudine),[13,14] (1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol (ABC, abacavir)[15–17] and bis-(POC)PMPA (tenofovir disoproxil fumarate, viread)[18,19] (Fig. 1).

The drug d4T[13,14,20–27] is a very potent and selective inhibitor of reverse transcriptase and requires anabolic activation to the 5′-triphosphate derivative by cellular kinases. Despite its approval by the US FDA, d4T shows (i) instability in acidic media due to ready glycosyl bond cleavage, which limits its usefulness as an orally bioavailable drug; (ii) side effects; and (iii) resistance arising from amino acid mutations of reverse transcriptase. In an attempt to overcome these deficiencies and provide more extensive data for a wider structure–activity relationship (SAR) to be made, a number of analogues have been synthesised with functional groups other than protons at either or both of the 2′- and 3′-positions. For the sake of clarity, this review has been arranged to describe the synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides having (i) a branching group at either of the 2′- or 3′-positions other than a proton, and (ii) branching groups at both of the 2′- and 3′-positions other than protons. Various functionalities have been substituted at either the 2′- or 3′-position of d4Ns, which include halogeno, $N_3$, $CF_3$, CN, alkyl, alkenyl, alkynyl, aryl, thio and seleno groups. Perhaps the most sought-after targets, however, have been those possessing a fluorine atom at either of the 2′- or 3′-positions, since such substituted nucleosides are close analogues of d4T due to fluorine having a van der Waal's radius close to that of a hydrogen atom. In addition, it has been postulated that the introduction of a fluorine atom at either of the 2′- or 3′-positions of the glycone moiety could result in a stabilised glycosyl bond of d4Ns.

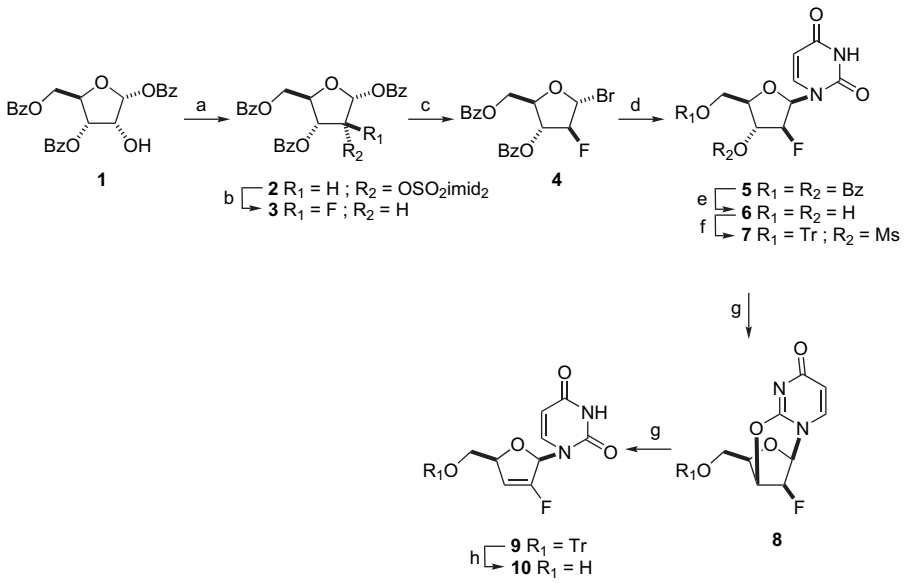
## 2. Synthesis of 2′- or 3′-branched 2′,3′-unsaturated nucleosides

### 2.1. Base-catalysed elimination

Several syntheses of 2′,3′-unsaturated nucleosides having various functional groups in either the 2′- or 3′-positions have been described, which involve base-catalysed cis- or trans-elimination. The trans-elimination can be effected with a nucleofuge (e.g., anhydro, halogen, mesyl or ester), which is either α or β to the required 2′- or 3′-branched group in the target compound. Examples of trans-eliminations in which the nucleofuge is β to either a 2′- or 3′-branched group are as follows. Martin et al. reported the synthesis of the 2′-fluoro-2′,3′-unsaturated uracil **10**[28] via the dihalogeno sugar **4**.[29] Starting from the D-ribose derivative **1**, the subsequent imidazolylsulfonate **2** was fluorinated with $KHF_2$ and HF to afford **3** in 63% yield, which was then converted into the dihalogeno sugar **4** in 98% yield. *N*-Glycosylation with silylated uracil gave the nucleoside **5**, which was treated with methanolic ammonia to give the fully deprotected 2′-deoxyuridine **6** in 69% yield (two steps). Treatment of **6** with trityl chloride in pyridine followed by methanesulfonyl chloride gave **7**, which, on brief treatment with aqueous sodium hydroxide, gave the anhydronucleoside **8**. With or without isolation, further treatment of **8** with sodium hydroxide gave the olefin **9**, which was deprotected with HCl in chloroform to afford the target nucleoside **10** in 35% yield (two steps) (Scheme 1).

The methodology of Horwitz et al.[30–34] has been used by different research groups to obtain **14–16** via the *O*-2,3′-anhydroxylo- derivatives **11–13** using potassium *tert*-butoxide in DMSO to deprotonate at the C-2′-position in 75–92% yields (Table 1).

Altona et al. reported the dehydrohalogenation of nucleoside analogues in basic media.[37] Starting from the D-arabinose



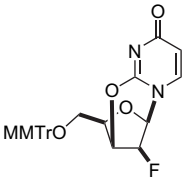
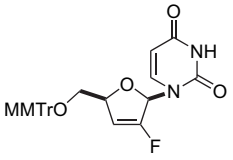
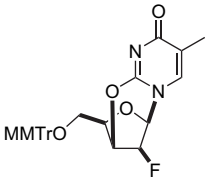
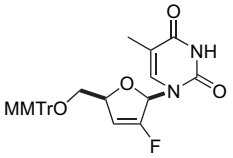
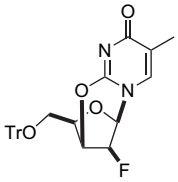
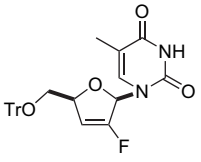

**Scheme 1**. Reagents and conditions: (a) NaH, $(Imid)_2SO$, DMF (85%); (b) $KHF_2$, butan-1,3-diol then HF, $H_2O$ (63%); (c) HBr, AcOH, $CH_2Cl_2$ (98%); (d) silylated uracil, $CHCl_3$ (78%); (e) $NH_3$, MeOH (88%); (f) TrCl, pyridine then MsCl (86%); (g) NaOH, $H_2O$, EtOH (54%); (h) HCl, $CHCl_3$ (64%).

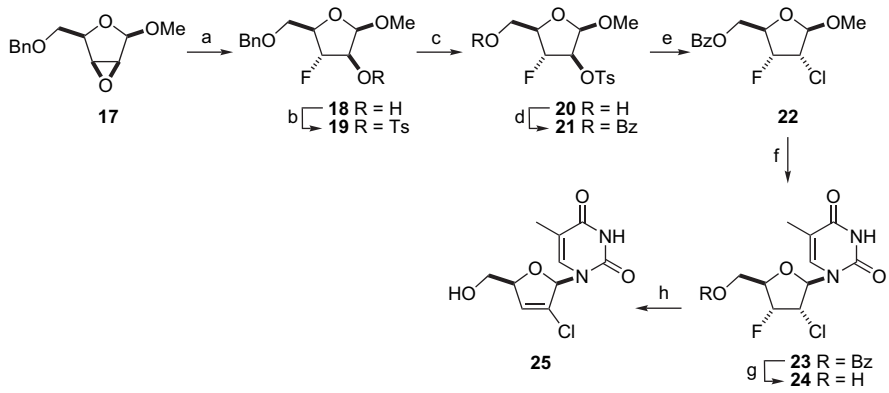
derivative **17**, treatment with $KHF_2$ and NaF in 1,2-ethylene glycol afforded the fluoride **18** in 31% yield.[38] Debenzylation of the tosylate **19** and subsequent benzoylation of the primary hydroxyl group in **20** provided the glycoside **21**. Replacement of the tosyloxy group of **21** by a chlorine atom using LiCl in DMSO gave the riboside **22** in 72% yield. *N*-Glycosidation of **22** with silylated thymine and subsequent deprotection of the 5′-position in **23** afforded the nucleoside **24** in 30% yield (two steps). Treatment of **24** with MeONa in methanol then gave the corresponding chloro olefin **25** in 47% yield (Scheme 2).

A similar elimination has been applied to purine nucleosides such as adenine **27** to give the target nucleoside **28** in 77% yield. It is notable that a slightly higher yield (82% vs 77%) was obtained starting from the dibenzoylated adenine derivative **26** (Scheme 3).

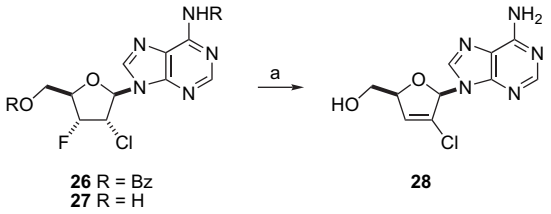
In accordance with the greater strength of the C–F bond (105.5 kcal/mol), compared to that of the C–Cl bond (78.5 kcal/mol), elimination of HCl was expected. Altona et al. suggested that a likely explanation of the HF versus HCl elimination was the conformational peculiarities of the starting nucleoside **24**. In the conformation of the D-ribofuranose ring ($^2$E: $150<P<162$), the $F_{3'}$ and $H_{2'}$ atoms are trans oriented (antiperiplanar, ap), whereas the $Cl_{2'}$ atom and $H_{1'}$ and $H_{3'}$ atoms are *gauche* arranged (synclinal, sc) (Fig. 2).

**Table 1**. Synthesis of 2′-fluoro nucleosides **14–16** starting from the corresponding *O*-2,3′-anhydro nucleosides **11–13**

| Entry | | Starting material | | Olefin | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| 1 | **11** |  | **14** |  | 84 | 35 |
| 2 | **12** |  | **15** |  | 75 | 35 |
| 3 | **13** |  | **16** |  | 92 | 36 |




**Scheme 2**. Reagents and conditions: (a) $KHF_2$/NaF, 1,2-ethylene glycol (31%); (b) TsCl, pyridine (89%); (c) $H_2$, Pd/C, EtOH (88%); (d) BzCl, pyridine (81%); (e) LiCl, DMSO (72%); (f) silylated thymine, TMSOTf, MeCN (55%); (g) $NH_3$, MeOH (55%); (h) MeONa, MeOH (47%).




**Scheme 3**. Reagents and conditions: (a) MeONa, MeOH (from **27**: 77%; from **26**: 82%).

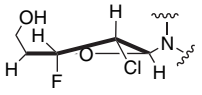
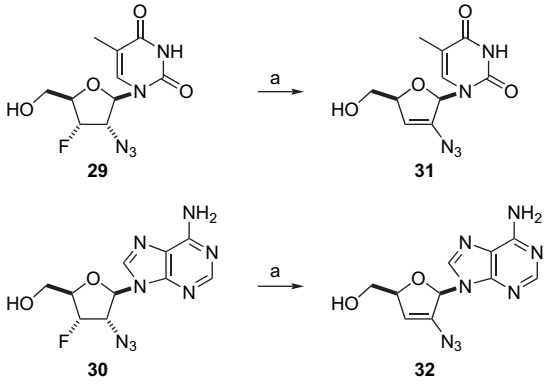


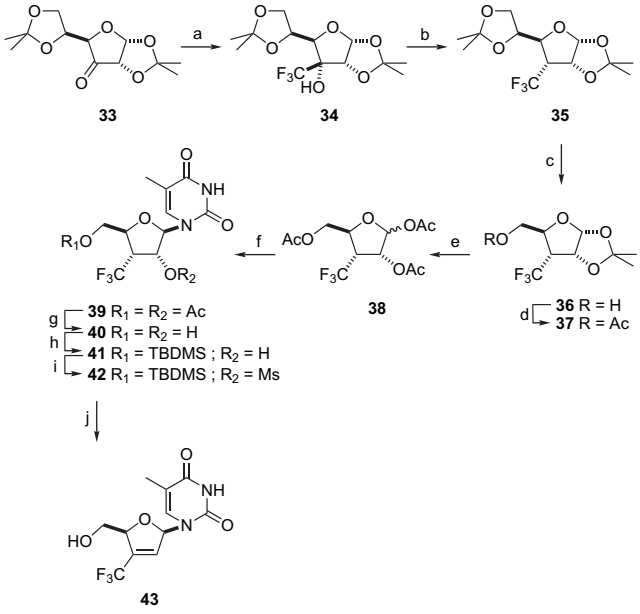

**Figure 2**. Conformation of the glycone moiety of the nucleoside **24**.

In accordance with the above method,[37] treatment of the nucleosides **29** and **30** afforded the vinyl azides **31** and **32** in 47% and 69% yields, respectively (Scheme 4).




**Scheme 4**. Reagents and conditions: (a) MeONa, MeOH (from **29**: 47%; from **30**: 69%).

Application of this strategy was described by Portella et al.[39] for the synthesis of 3′-*C*-trifluoromethyl d4T (**43**) (Scheme 5) and the d4U analogue **44** (Fig. 3). Starting from the D-glucose derivative **33**, trifluoromethylation with TFMTMS and subsequent desilylation gave the trifluoromethyl derivative **34** in 88% yield.[40] The *allo*-derivative **35** was obtained in two steps by methyloxylation and classical radical deoxygenation. Selective hydrolysis of the 5,6-ketal group on **35** followed by periodic oxidation and $NaBH_4$ reduction provided the *ribo*-derivative **36** in 68% yield (three steps). To preserve the furanose form, acetylation of the primary hydroxyl group of **36** was effected to give **37**, which, upon subsequent hydrolysis with aqueous $CF_3COOH$ and acetylation with $Ac_2O$, pyridine and DMAP, yielded the two anomers **38**




**Scheme 5**. Reagents and conditions: (a) TFMTMS, TBAF, THF then TBAF, MeOH (88%); (b) 1. MeOCOCOCl, pyridine, $CH_2Cl_2$; 2. $Bu_3SnH$, AIBN, toluene (73%); (c) 1. $H_2SO_4$, MeOH, dioxane; 2. $NaIO_4$, $H_2O$ then $NaBH_4$, $H_2O$, MeOH (68%); (d) $Ac_2O$, pyridine, $CH_2Cl_2$ (90%); (e) 1. $CF_3COOH$, $H_2O$; 2. $Ac_2O$, DMAP, pyridine (93%); (f) silylated thymine, TMSOTf, MeCN (95%); (g) MeONa, MeOH (91%); (h) TBDMSCl, DMAP, pyridine, $CH_2Cl_2$ (70%); (i) MsCl, pyridine, $CH_2Cl_2$ (100%); (j) TBAF, THF (69%).

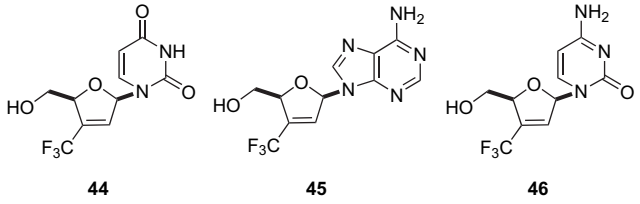
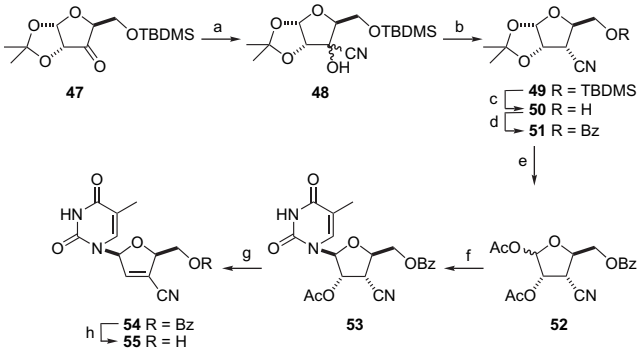



**Figure 3**. 3′-*C*-Trifluoromethyl nucleosides **44**–**46**.

in 84% yield (three steps). *N*-Glycosylation of the acetates **38** with silylated thymine provided the nucleoside **39**, stereospecifically, in 95% yield. After deacetylation to give **40** and selective silylation to form **41**, mesylation of **41** afforded the corresponding ester **42** in 64% yield (three steps). The elimination step was performed smoothly with TBAF, which induced desilylation and subsequent elimination leading to the target nucleoside **43** in 69% yield (Scheme 5).

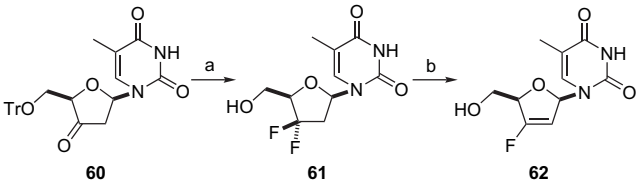
Similar eliminations were reported by Mathé et al.[41] for the synthesis of the adenosine and cytosine derivatives **45** and **46** (Fig. 3).

Chu et al. described the synthesis of different 3′-*C*-cyano-3′-deoxyribonucleosides[42] using an acetyloxy group as a nucleofuge. Treatment of the 3′-keto nucleoside **47** with NaCN in a mixture of aqueous $NaHCO_3$ and $Et_2O$ afforded the cyanohydrin **48** as an epimeric mixture.[43] Classical Barton deoxygenation provided the 3-*C*-cyano-3-deoxy derivatives **49** and subsequent protection/deprotection steps on **50**/**51** afforded the diacetate **52** in 54% overall yield. *N*-Glycosylation with the silylated thymine afforded the nucleoside **53** stereoselectively, and this was treated with DBU and DMAP in dichloromethane to give the 2′,3′-unsaturated nucleoside **54** in 83% yield (two steps). Careful deprotection of the primary hydroxyl group afforded the target nucleoside **55** in 68% yield (Scheme 6). Introduction of uracil, cytosine, adenosine and guanosine into the diacetate **52**, followed by mild base-catalysed elimination, gave the corresponding nucleosides **56**–**59** (Fig. 4).



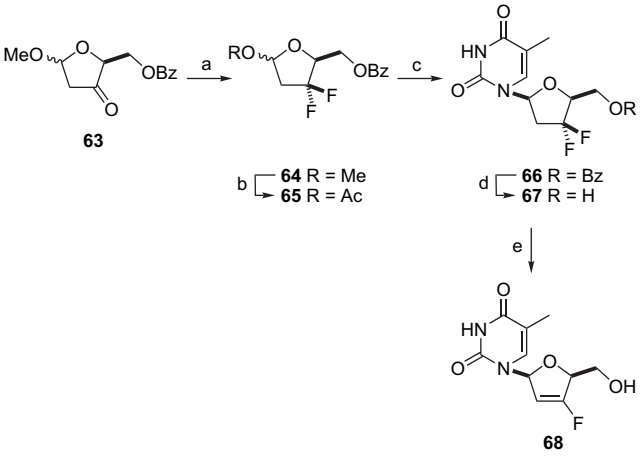

**Scheme 6**. Reagents and conditions: (a) Ref. 46; (b) 1. PhO(CS)Cl, DMAP, $CH_2Cl_2$; 2. AIBN, $Bu_3SnH$, toluene (68%); (c) HCl, MeOH (66%); (d) BzCl, pyridine (95%); (e) 1. TFA, $H_2O$; 2. $Ac_2O$, pyridine (90%); (f) BSA, thymine, TMSOTf, MeCN (86%); (g) DMAP, BDU, $CH_2Cl_2$ (96%); (h) $K_2CO_3$, MeOH (68%).

Examples of trans-eliminations with the nucleofuge α to either the 2′- or 3′-branched group have also been described. Herdewijn et al.[44] reported the synthesis of 3′,3′-difluoro-2′,3′-dideoxythymidine (**61**), starting from the corresponding 3′-ketothymidine **60** by treatment with DAST, similar to that described by Bergstrom.[45] Treatment of the *gem* difluoro compound **61** with sodium methoxide in anhydrous dimethylformamide yielded the target nucleoside **62** in 62% yield (Scheme 7).




**Scheme 7**. Reagents and conditions: (a) Ref. 45; (b) MeONa, MeOH (62%).

Chu et al. developed this type of strategy to effect a more general synthetic methodology, as exemplified by the introduction of the 3′,3′-difluoro functionality into a glycone moiety before condensation with a heterocyclic base.[46,47] Thus, treatment of the 3-keto derivative **63** with DAST afforded the 3,3-difluoro analogue **64**, which was transglycosylated to the acetate **65** in 63% overall yield. Condensation of **65** with silylated thymine in the presence of TMSOTf gave the corresponding nucleosides **66** and deprotection of the 5′-hydroxyl group followed by treatment of **67** with sodium methoxide afforded the target nucleoside **68** in 16% yield (three steps) (Scheme 8).




**Scheme 8**. Reagents and conditions: (a) DAST, $CH_2Cl_2$ (66%); (b) $Ac_2O$, $H_2SO_4$, AcOH (95%); (c) silylated thymine, TMSOTf, MeCN (53%); (d) $NH_3$, MeOH (55%); (e) MeONa, DMF (62%).

Application of this strategy permitted different L-2′,3′-didehydro-2′,3′-dideoxy-3′-fluoronucleosides **69**–**72** to be obtained (Fig. 5).

In order to provide compounds for an extended SAR study, Chu et al. reported the synthesis of the corresponding D-enantiomers,[48] starting from D-mannitol (**73**). After diacetalisation of **73** and oxidative cleavage, the D-glyceraldehyde

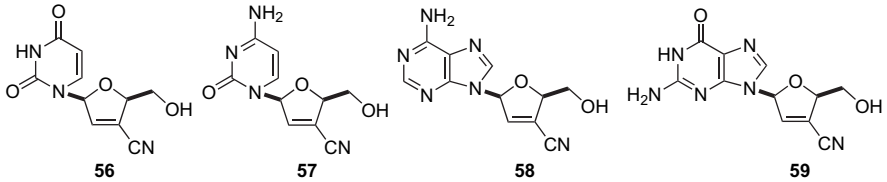



**Figure 4**. 3′-*C*-Cyano L-nucleosides **56**–**59**.

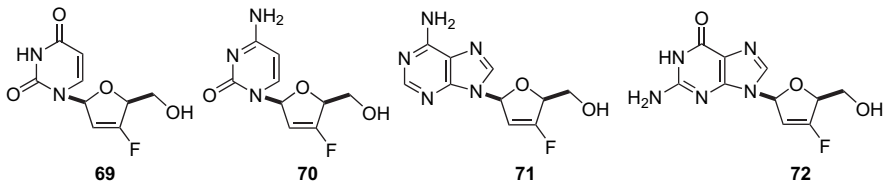
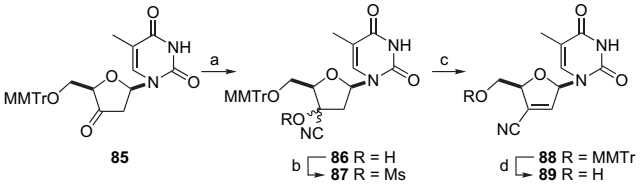



**Figure 5**. 3′-*C*-Fluoro L-nucleosides **69–72**.

derivative **74** was reacted with (1,3-dioxolan-2-ylmethyl)-magnesium bromide to give the alcohol **75** in 94% yield. Following Swern oxidation of **75**, the resulting ketone **76** was treated with DAST to yield the difluorinated intermediate **77** in 51% yield. Selective deprotection, benzoylation of the primary hydroxyl group in **78** and acidic treatment of **79** afforded the epimeric acetates **80** in 73% yield (four steps). These key and versatile epimeric acetates provided ready access to the D-2′,3′-didehydro-2′,3′-dideoxy-3′-fluoro-nucleosides **62** and **81–84** (Scheme 9) to complement the L-analogues **68–72**, thus providing a more systematic SAR investigation to be made.

Chattopadhyaya et al. reported the synthesis of the 3′-*C*-cyano-2′,3′-unsaturated nucleosides **89**[49] in which the 3′-keto-thymidine **85** was treated with sodium cyanide and sodium bicarbonate in an ethyl acetate–water mixture to afford the two epimers **86** in 70% yield. The unseparated epimeric nitriles **86** were treated with methylsulfonyl chloride in pyridine to afford the 3′-*C*-cyano-mesylates **87**, which underwent base-catalysed elimination using a refluxing mixture of pyridine and triethylamine to give the 2′,3′-unsaturated nucleosides **88** in 46% overall yield (three steps). Subsequent deprotection of the primary hydroxyl group gave the target nucleoside **89** in 88% yield (Scheme 10).

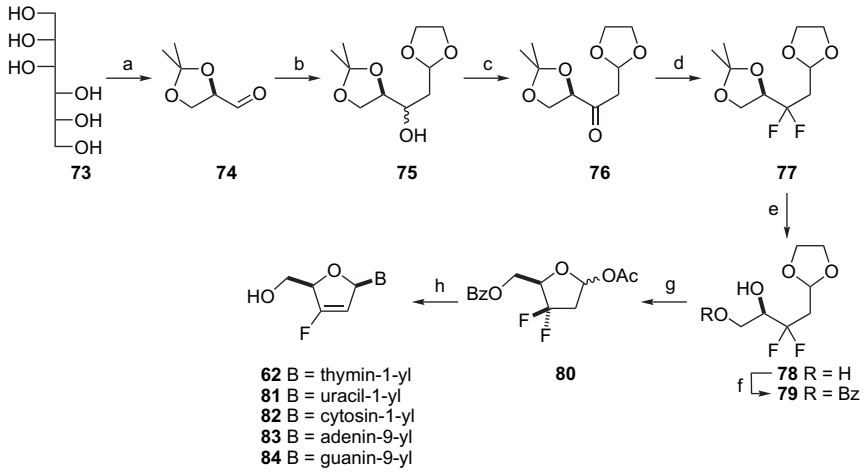
Krayesvsky et al. described the synthesis of the hydrolytically unstable nucleoside **95** starting from the ketone **90** (Scheme 11).[50] Thus, the reaction of **90** with MeMgI and MeI provided the 3-*C*-methyl derivative **91** in 83% yield with complete stereoselectivity. After benzoylation of the tertiary hydroxyl group, condensation of the resulting ester



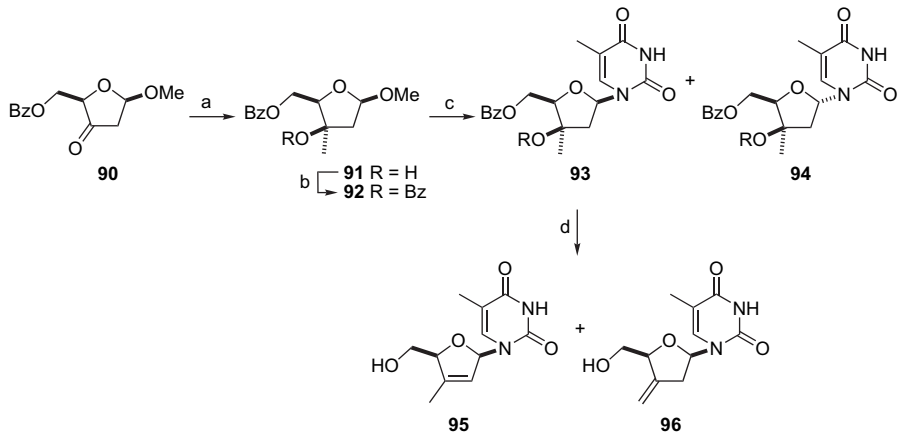

**Scheme 10**. Reagents and conditions: (a) NaCN, $NaHCO_3$, ethyl acetate, $H_2O$; (b) MsCl, pyridine; (c) $Et_3N$, pyridine (from **85**: 46%, three steps); (d) AcOH, $H_2O$ (88%).

**92** with silylated thymine gave both anomers **93** and **94** due to the lack of neighbouring group participation. Separation of the anomers required the deprotection of **93** and **94** to enable efficient chromatographic resolution followed by re-benzoylation. The target nucleosides, 3′-*C*-methyl derivative **95** and the 3′-*C*-methylene derivative **96**, were obtained in 34% and 11% yields, respectively, by treating the corresponding precursors **93** and **94** with thionyl chloride followed by ammonia in methanol to effect elimination and deprotection.

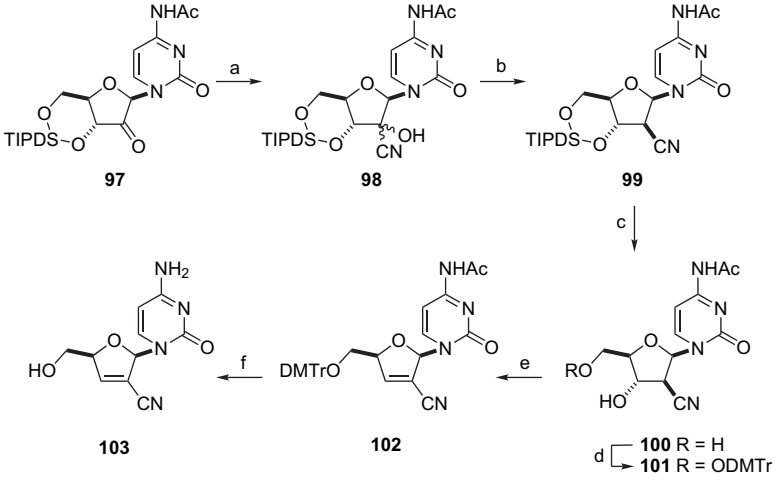
In contrast to the trans-eliminations seen in these types of nucleosides, the alternative cis-eliminations are only effected when the nucleofuge is β to either the 2′- or 3′-branched group. These are exemplified in the synthesis of the nucleoside **103**, starting from the 2′-keto nucleoside **97**. The starting material was treated with NaCN in a mixture of aqueous $NaHCO_3$ and $Et_2O$ to afford the cyanohydrins **98** in 98% yield as an isomeric mixture (Scheme 12). This was treated, firstly, with phenyl chlorothionoformate in the presence of triethylamine and DMAP in MeCN to give the




**Scheme 9**. Reagents and conditions: (a) 1. acetone, $H_2SO_4$; 2. $NaIO_4$, $H_2O$; (b) (1,3-dioxolan-2-ylmethyl)magnesium bromide, THF (94%); (c) $(ClCO)_2$, $Et_3N$, DMSO (95%); (d) DAST, $CH_2Cl_2$ (51%); (e) HCl, dioxane (90%); (f) BzCl, pyridine (85%); (g) 1. HCl, MeOH; 2. $Ac_2O$, $H_2SO_4$, AcOH (95%); (h) 1. silylated heterocyclic bases, TMSOTf, MeCN; 2. $NH_3$, MeOH; 3. MeONa, DMF.




**Scheme 11**. Reagents and conditions: (a) MeMgI, MeI, $Et_2O$ (83%); (b) BzCl, *N*-methylimidazole (54%); (c) 1. silylated thymine, TMSOTf, $C_2H_4Cl_2$; 2. MeONa, MeOH (for **93**: 34%; for **94**: 47%, two steps), (chromatographic separation of anomers); 3. BzCl, pyridine (95%); (d) 1. $SOCl_2$; 2. $NH_3$, MeOH (for **95**: 34%; for **96**: 11%, two steps).




**Scheme 12**. Reagents and conditions: (a) NaCN, $H_2O$, EtOH (98%); (b) 1. PhO(CS)Cl, $Et_3N$, DMAP, MeCN; 2. $Bu_3SnH$, AIBN, toluene (73%); (c) TBAF, AcOH, THF (84%); (d) DMTrCl, pyridine (83%); (e) $(Imid)_2CS$, DMF (73%); (f) 1. AcOH, $H_2O$ (69%); 2. HCl, MeOH (66%, two steps).

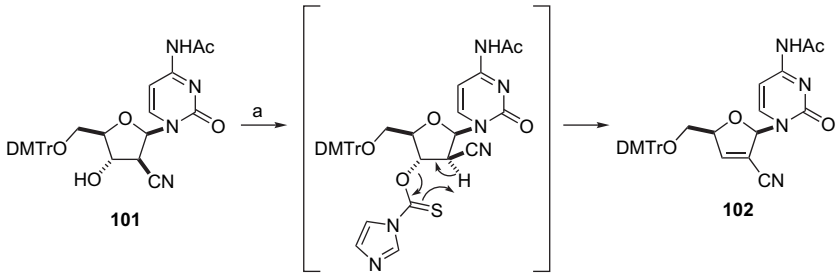
corresponding thiocarbonate, which was not purified, and, secondly, with $Bu_3SnH$ in the presence of AIBN in toluene to effect radical deoxygenation and, as a consequence, the cyano derivative **99** in 73% yield (two steps) as the sole product, due to steric hindrance of the β face. Classical removal of the silyl protecting group of **99** afforded compound **100**, which was treated with dimethoxytrityl chloride to give the protected derivative **101** in 83% yield. Reaction of **101** with *N*,*N*′-thiocarbonyldiimidazole in DMF furnished the β-elimination product **102** in 73% yield without isolation of the carbonylimidazole ester intermediate. Detritylation and deacetylation of **102** gave the target nucleoside **103** in 66% yield (two steps).[51,52]

The cis-elimination seen in the conversion of **101** into **102** is likely to be due to intramolecular participation of the thiocarbonyl group with the 2′-proton of the thionocarbonate intermediate, as illustrated in the mechanism depicted in Scheme 13.

cis-Elimination was found to proceed more smoothly using a thionocarbonate than with either a carbonate or an ester, where more forcing conditions were required. As well as introducing the thiocarbonyl group with *N*,*N*′-thiocarbonyldiimidazole in DMF, phenyloxythiocarbonyl chloride and DMAP in acetonitrile have additionally been employed, with the subsequent thiocarbonate derivatives **104**–**106** also undergoing efficient *syn*-eliminations in the 2′- and 3′-positions to give **107**–**109** (Table 2).

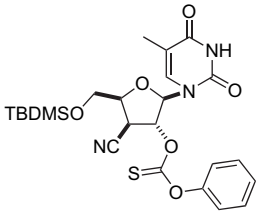
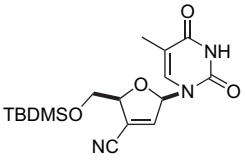
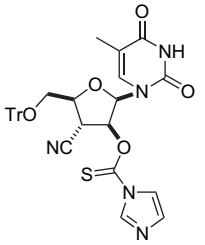
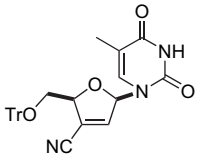
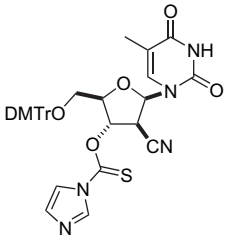
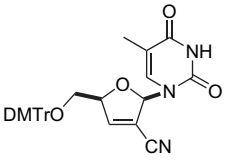
Other cis-elimination reactions have employed the methylsulfonyl group as a nucleofuge. Martin et al. described the synthesis of the 2′-fluoro nucleoside **16**[28] directly from the mesyl derivative **110**. It is notable that the corresponding *O*-2,3′-anhydro pyrimidine was not formed in the reaction. Deprotection of **16** with acid gave the 2′,3-unsaturated nucleoside **111** (Scheme 14).

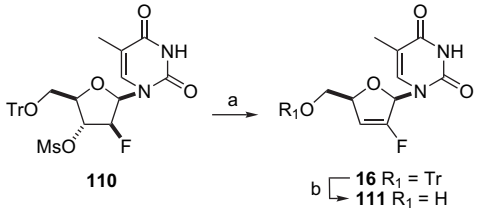
A number of routes involving a cis-elimination step have used 2′,3′-epoxides as the starting materials. Faul et al. described the synthesis of a 3′-*C*-cyano-2′,3′-unsaturated nucleoside **114**, which also makes use of a mesyl nucleofuge.[55] Reaction of the epoxide **112** with LiCN introduced the cyano group into the $C_{3'}$ position, thus giving **113**. Subsequent mesylation of the secondary hydroxyl group in the presence of triethylamine and ethyl acetate afforded the



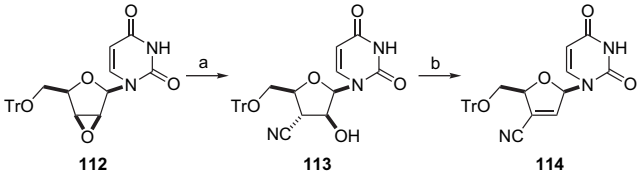

**Scheme 13**. Reagents and conditions: (a) $(Imid)_2CS$, DMF (73%).

**Table 2**. Synthesis of *C*-cyano nucleosides **107–110** from the corresponding thiocarbonyl derivatives **104–106**

| Entry | | Substrate | | Olefin | Yield (%) | Refs. |
|---|---|---|---|---|---|---|
| 1 | **104** |  | **107** |  | 80 | 53 |
| 2 | **105** |  | **108** |  | nd | 54 |
| 3 | **106** |  | **109** |  | 84 | 52 |




**Scheme 14**. Reagents and conditions: (a) NaOH, $H_2O$, EtOH (55%); (b) HCl, $CHCl_3$ (78%).

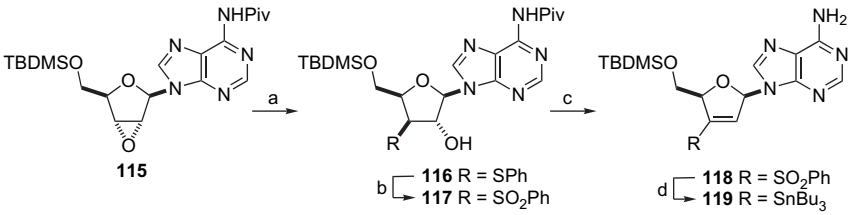



**Scheme 15**. Reagents and conditions: (a) LiCN, THF (68%); (b) MsCl, $Et_3N$, ethyl acetate (81%).

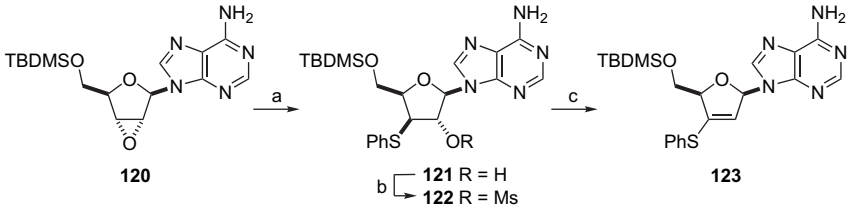
2′,3′-unsaturated nucleoside **114** in 55% overall yield (Scheme 15).

Tanaka et al. described the synthesis of 3′-*C*-stannyl-d4A (**119**) by radical-mediated desulfonylative stannylation.[56] Starting from the epoxide **115**, ring opening was followed by MCPBA oxidation of **116** to give the β-hydroxysulfone product **117** in 90% yield. Deprotection of the amino group of the aglycone and subsequent methylsulfonylation directly afforded the cis-elimination product **118** in 81% yield (two steps). Radical-mediated desulfonylative stannylation of **118** proceeded efficiently by reacting with $Bu_3SnH$ in the presence of AIBN and triethylamine in refluxing benzene to give the 3′-*C*-stannyl nucleoside **119** in 76% yield (Scheme 16). This result was in accordance with the work described by Chattopadhyaya et al. using uracil and adenine analogues.[57]

Application of this strategy permitted the synthesis of the corresponding *C*-phenylthio derivative **123** from **120** (Scheme 17).[56] Mesylation of the nucleoside **121** gave the




**Scheme 16**. Reagents and conditions: (a) PhSH, MeONa (90%); (b) MCPBA, MeOH (100%); (c) 1. $NH_3$, MeOH; 2. $MeSO_2Cl$, DMAP, pyridine (81%); (d) $Bu_3SnH$, AIBN, $Et_3N$, benzene (76%).




**Scheme 17**. Reagents and conditions: (a) PhSH, MeONa (100%); (b) MsCl, DMAP, pyridine (98%); (c) DBN, MeCN (78%).

corresponding sulfonyl ester **122** in excellent yield (98%), which subsequently underwent cis-elimination with DBN in refluxing acetonitrile to afford the vinyl sulfide **123** in 78% yield. It is notable, in this example, that the acidity of the $H_{3'}$ proton was insufficient to allow spontaneous cis-elimination to take place.

Chattopadhyaya et al. reported similar work for the synthesis of the 3′-*C*-seleno derivative **127** starting from the epoxide **124** (Scheme 18).[58] Ring opening of **124** to form **125** and subsequent mesylation gave the 3′-*C*-seleno derivative **126** in 49% yield. Treatment of **126** in basic conditions afforded the cis-elimination product **127** in 92% yield. Starting from compound **127**, the oxidation with MCPBA gave the 3′-*C*-selenonyl derivative **128** in 83% and deprotection of the primary hydroxyl group of **128** in acidic conditions afforded the target nucleoside **129** in 97% yield.

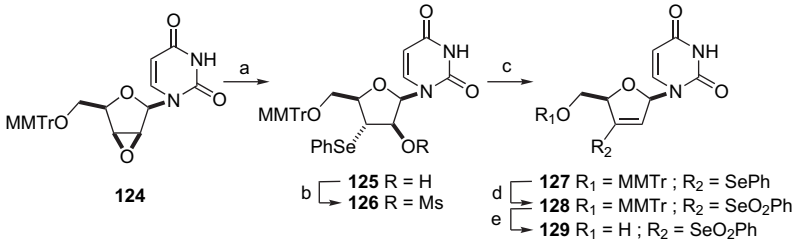
## 2.2. Oxidative elimination

The synthesis of 2′,3′-unsaturated nucleosides has been reported using selenoxide elimination under mild conditions. Tanaka et al. described the synthesis of 2′-*C*- and 3′-*C*-branched 2′,3′-unsaturated nucleosides via a β-hydroxyselenide intermediate **132** (Scheme 19).[59,60] Walden inversion at the 3′-position by treatment of the 3′-*O*-mesyl derivative **130** with $(PhSe)_2$ and $NaBH_4$ in refluxing THF–ethanol gave the corresponding selenide **131** in 81% yield. Conversion of compound **131** into the β-hydroxyselenide **132** was effected in almost quantitative yield by deacetylation followed by selective silylation of the primary hydroxyl group. When the nucleoside **132** was brominated in $CCl_4$ with $SOBr_2$ in the presence of imidazole, a mixture of β-bromoselenides **133** and **134** was obtained in 72% yield. This mixture was subjected to selenoxide elimination in $CH_2Cl_2$ by treatment with MCPBA to provide the corresponding bromovinyl nucleosides **135** and **136**, which were separated by column chromatography in 42% and 38% yields, respectively.

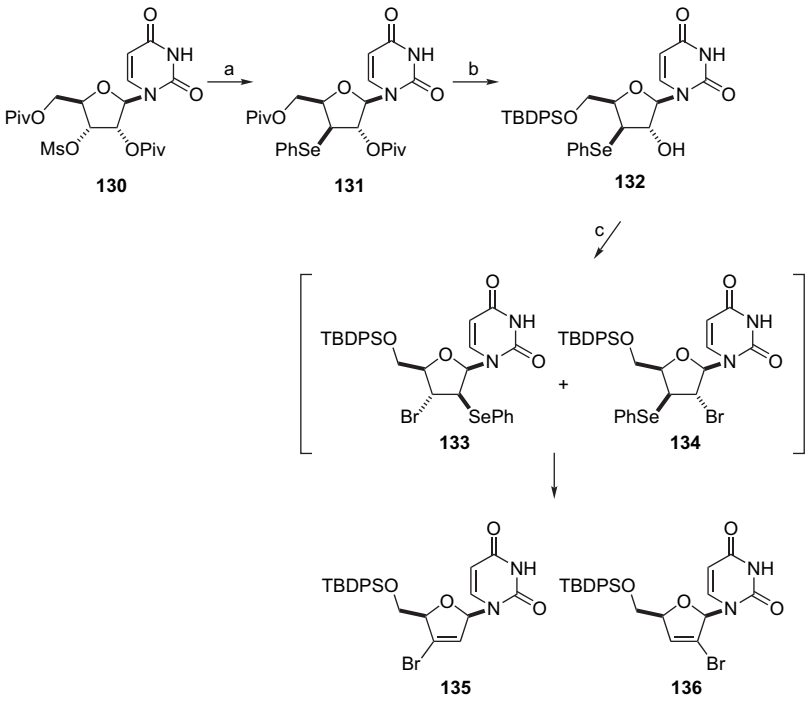
The authors proposed that the regioisomers **133** and **134** were obtained via a 2′,3′-up seleniranium intermediate, which then underwent ring opening by bromide ions at the α-face (Scheme 20).

Application of the aforementioned strategy permitted the synthesis of the adenine analogues **137** and **138** in 41% and 33% yields, respectively (Fig. 6).[60]

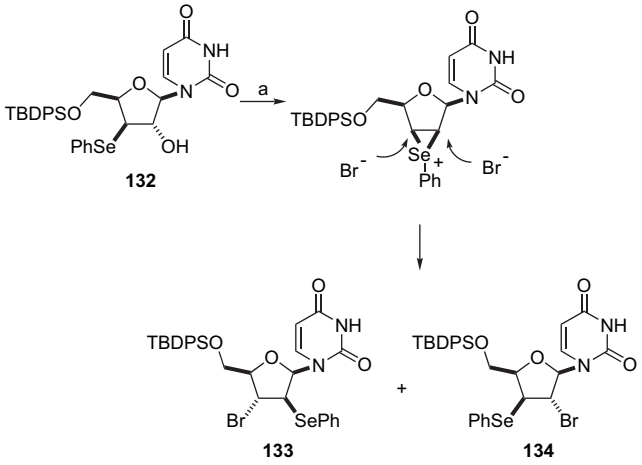
A similar cis-elimination involving selenoxide fragmentation was observed by Myasaka et al., in which the unstable enol ester **140** was detected by NMR spectroscopy, as an intermediate in the conversion of the selenide derivative **139** into the ketone **141** by reaction with MCPBA. It is notable that attempts to isolate the intermediate enol acetate **140** by chromatographic purification were unsuccessful (Scheme 21).[61]




**Scheme 18**. Reagents and conditions: (a) $(PhSe)_2$, $LiAlH_4$, THF (55%); (b) MsCl, pyridine (89%); (c) *t*-BuOK, DMF (92%); (d) MCPBA, MeOH (83%); (e) AcOH, $H_2O$ (97%).




**Scheme 19**. Reagents and conditions: (a) $(PhSe)_2$, $NaBH_4$, THF, EtOH (81%); (b) 1. NaOH, $H_2O$; 2. TBDPSCl, pyridine (96%); (c) 1. imidazole, $CCl_4$, $SOBr_2$ (72%); 2. MCPBA, $CHCl_3$ (for **135**: 42%; for **136**: 38%).




**Scheme 20**. Reagents and conditions: (a) imidazole, $CCl_4$, $SOBr_2$.

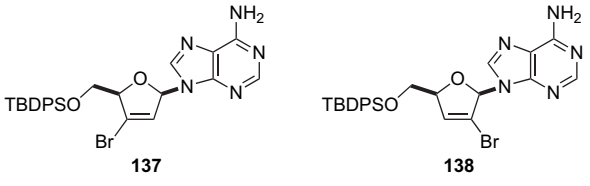


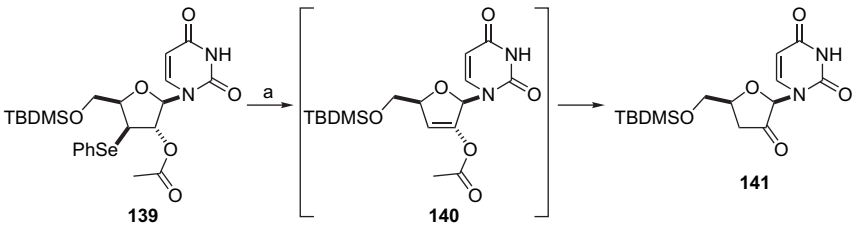

**Figure 6**. Bromovinyl nucleosides **137** and **138**.

Chen et al. described the synthesis of 2′-fluoro-2′,3′-dideoxy-2′,3′-didehydro-L-nucleosides using oxidative elimination of the 2′-phenylseleno intermediate **144** (Scheme 22).[62] Stereospecific introduction of the 2′-phenylseleno moiety into **142** afforded the 2′-α-phenylselenolactone **143** in 60% yield. Treatment of **143** with LiHMDS in THF followed by fluorination in the presence of $FN(SO_2Ph)_2$ provided the 2′-α-fluorinated lactone **144** in 86% yield. Subsequent oxidative elimination of the 2′-phenylseleno derivative **144** provided the 2′-fluoro-enonelactone **145** in 90% yield. Reduction of **145** with DIBALH and acylation of the resulting lactol **146** with acetic anhydride afforded an anomeric mixture of acetates **147** in 96% yield. *N*-Glycosylation of **147** with silylated thymine gave the nucleoside analogues **148** and **149** and subsequent deprotection of the primary hydroxyl group afforded the target nucleoside **150** in 38% yield and the corresponding anomer **151**. Application of this procedure for different heterocyclic bases furnished the nucleosides **152–154** (Fig. 7).

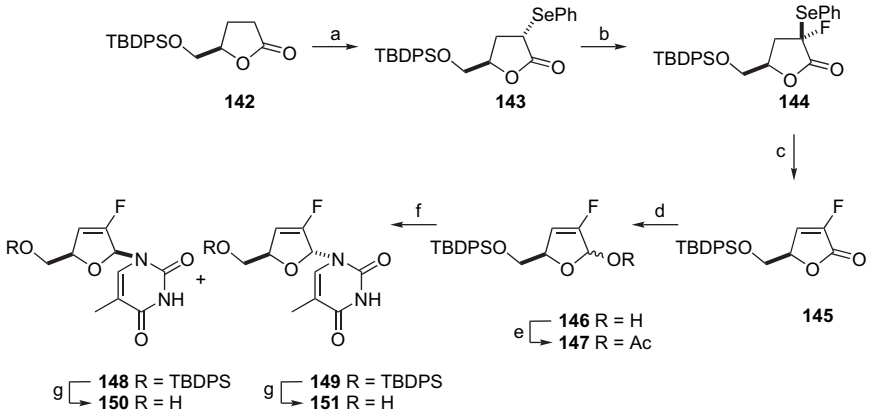
## 2.3. Hetero-Cope rearrangement

Different research groups have applied a hetero-Cope rearrangement of allylic nucleosides to obtain 3′-*C*-branched 2′,3′-unsaturated nucleosides. Matsuda et al. described the Wittig olefination of the 2′-keto nucleoside **155** to afford the methylidene nucleoside **156** in quantitative yield,[63] which, following desilylation to **157** and subsequent carbamoylation in the presence of 1,1′-thiocarbonyldiimidazole in DMF, afforded the 3′-imidazolylcarbonylthiomethyl derivative **158** resulting from an allylic rearrangement. Barton deoxygenation of **158** with $Bu_3SnH$ and AIBN in toluene and subsequent deprotection of the primary hydroxyl group provided the 3′-methyl derivative **95** in 45% yield (two steps) (Scheme 23). Matsuda et al. reported in the same paper[63] that deoxygenation of the 2′-*O*-methyloxalyl ester **160** by a Barton deoxygenation afforded the *endo* olefin **159** in 91% yield. It was proposed by the authors that the allyl radical intermediate **161** was involved in the conversion of each of the nucleosides **158** and **160** into the elimination product **159** (Scheme 24).

Czernecki et al. applied the aforementioned strategy by esterifying the 3′-methylidene nucleoside **162** to give the




**Scheme 21**. Reagents and conditions: (a) MCPBA, $CH_2Cl_2$.




**Scheme 22**. Reagents and conditions: (a) LiHMDS, THF, PhSeBr (60%); (b) LiHMDS, $FN(SO_2Ph)_2$, THF (86%); (c) $H_2O_2$, pyridine (90%); (d) DIBALH, toluene (93%); (e) $Ac_2O$, $Et_3N$ (96%); (f) silylated thymine, TMSOTf, MeCN (55%); (g) $Et_3N(HF)_3$, THF (69%).

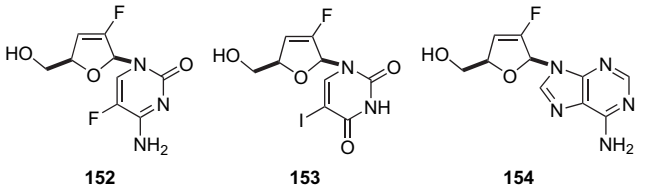
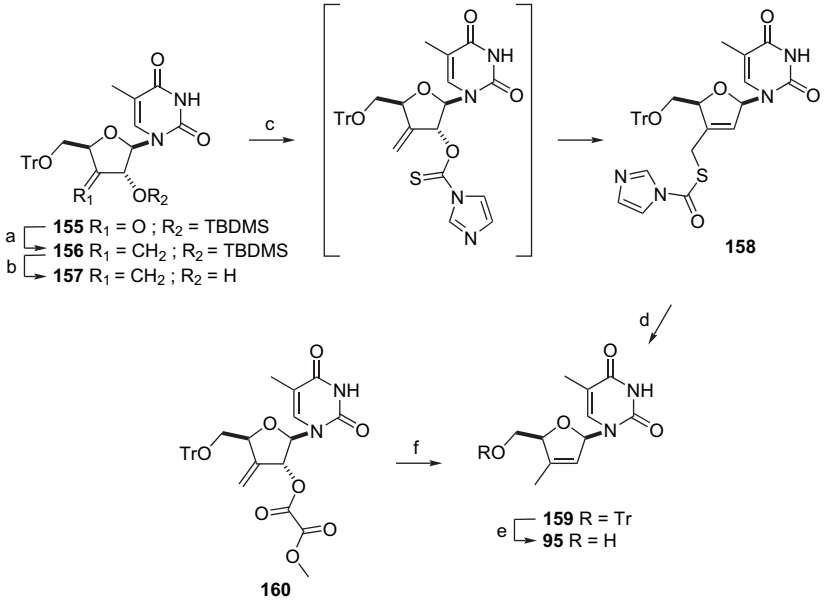


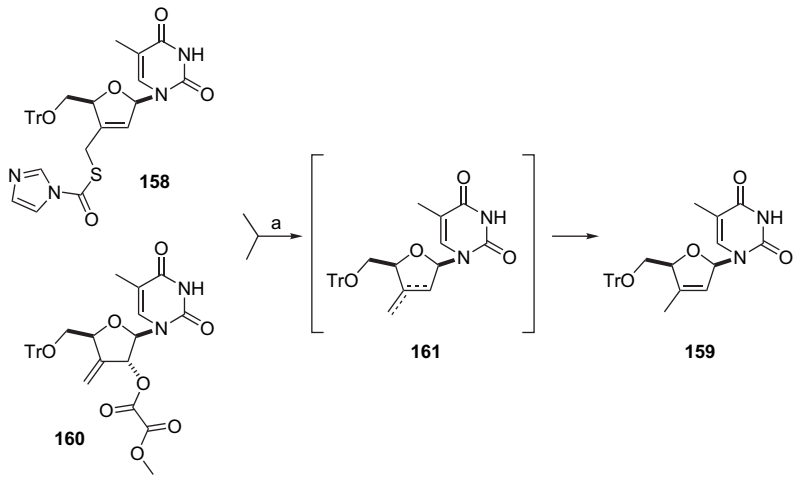

**Figure 7**. 2′-Fluoro L-nucleosides **152**–**154**.

phenoxythiocarbonyl allylic rearrangement product **163** in 49% yield. Barton deoxygenation to give **164** and deprotection of the primary hydroxyl group gave the target 2′,3′-unsaturated nucleoside **95** in 41% yield (Scheme 25).[64]

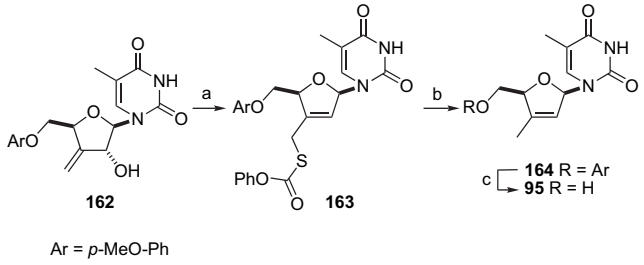
Czernecki et al. described the synthesis of various 3′-branched 2′,3′-unsaturated pyrimidine nucleosides by modification of the preceding methodology.[65] Treatment of the nucleosides **162** and **165** with triphenylphosphine in the




**Scheme 23**. Reagents and conditions: (a) $Ph_3PMeBr$, BuLi, THF (99%); (b) 1. TBAF, THF (99%); (c) $(Imid)_2CO$, DMF (84%); (d) $Bu_3SnH$, AIBN, toluene (83%); (e) HCOOH (54%); (f) $Bu_3SnH$, AIBN, toluene (91%).



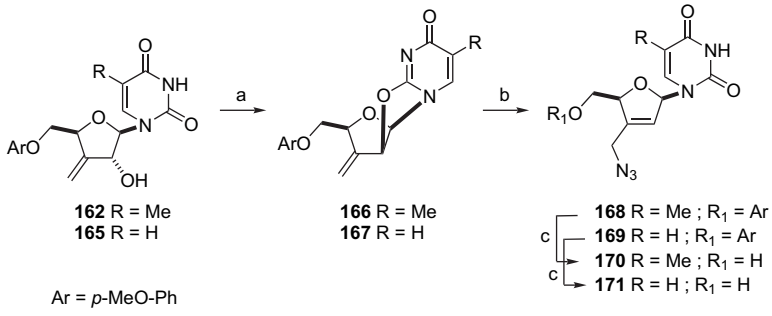

**Scheme 24**. Reagents and conditions: (a) $Bu_3SnH$, AIBN, toluene (from **158**: 83%; from **160**: 91%).



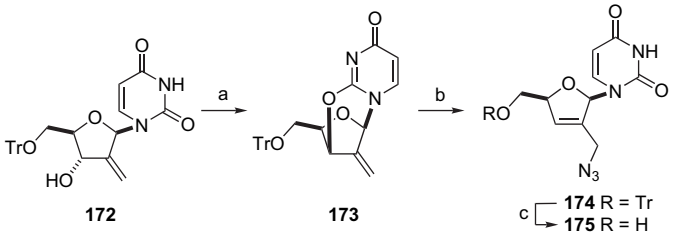

**Scheme 25**. Reagents and conditions: (a) PhO(CS)Cl, DMAP, pyridine (49%); (b) $Bu_3SnH$, AIBN, toluene (75%); (c) $(NH_4)_2Ce(NO_3)_6$, MeCN, $H_2O$ (55%).

presence of DEAD gave the 2,2′-anhydro derivatives **166** and **167** in 70% and 94% yield, respectively. Compounds **166** and **167** were each reacted with lithium azide in dimethylformamide to give **168** and **169** resulting from allylic rearrangement and 2,2′-anhydro ring opening. Subsequent deprotection of the primary hydroxyl group by oxidation with cerium ammonium nitrate furnished the target 2′,3′-unsaturated nucleosides **170** and **171** in 43% and 16% yield, respectively (two steps) (Scheme 26).

Application of this type of chemistry enabled the authors to obtain the 2′-*C*-branched counterpart **175**.[66] Starting from the 2′-*C*-methylidene derivative **172**, an intramolecular reaction was carried out to furnish the 2,3′-anhydro nucleoside **173** in 70% yield. Heating the nucleoside **173** in the presence of lithium azide in dimethylformamide resulted in the formation of the corresponding azido derivative **174** and deprotection of the 5′-position gave the target nucleoside **175** in low yield (8%) (two steps) (Scheme 27). It is notable that the azidation of the anhydro derivative **173** to give **174** resulted in a poor yield compared with that obtained for the nucleoside **169** (12% vs 85%).




**Scheme 26**. Reagents and conditions: (a) $PPh_3$, DEAD, DMF (for **166**: 70%; for **167**: 94%); (b) $LiN_3$, DMF (for **168**: 94%; for **169**: 85%); (c) $(NH_4)_2Ce(NO_3)_6$, MeCN, $H_2O$ (for **170**: 46%; for **171**: 19%).

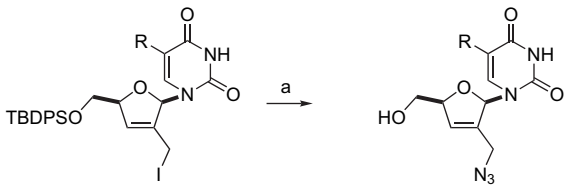



**Scheme 27**. Reagents and conditions: (a) $PPh_3$, DEAD, DMF (70%); (b) $LiN_3$, DMF (12%); (c) $BF_3$–$Et_2O$, $Et_3SiH$, MeCN (68%).

Samuelsson et al. described the synthesis of the 2′-*C*-methyl-substituted nucleosides **182** and **183** via alcohol transposition.[67] Starting from the 5′-*O*-silylated nucleosides **176** and **177**, the allylic iodides **178** and **179** were each obtained in 90% yield by reaction with chlorodiphenylphosphine in the presence of imidazole and iodine in a mixture of toluene–acetonitrile. Substitution of iodide in **178** and **179** by OAc using tetrabutylammonium acetate in methylene chloride gave **180** and **181**. Deprotection of the primary hydroxyl group in each of these compounds gave the target nucleosides **182** and **183** in 84% and 86% yield, respectively (Scheme 28).

Samuelsson et al.[67] proposed a plausible mechanism for the rearrangement obtained for the chlorodiphenylphosphine–iodine–imidazole system involved in the conversion of **177** into **179** (Scheme 29).

Using the same reagents, **178** and **179** were synthesised in a similar fashion. They were converted into the corresponding azides, which were subsequently deprotected to give the final nucleosides **184** and **175** (Scheme 30).



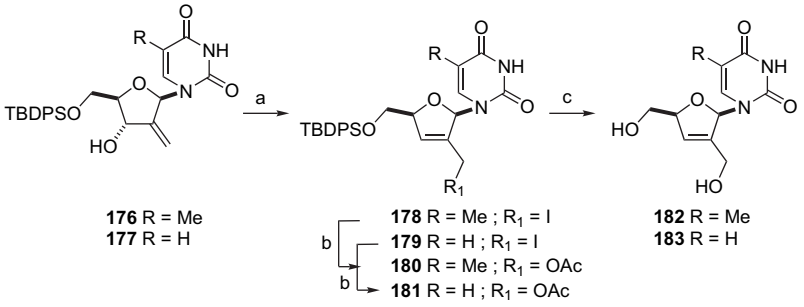

**Scheme 30**. Reagents and conditions: (a) 1. $NaN_3$, DMF; 2. TBAF, THF (for **184**: 96%; for **175**: 92%).

## 2.4. Cope elimination

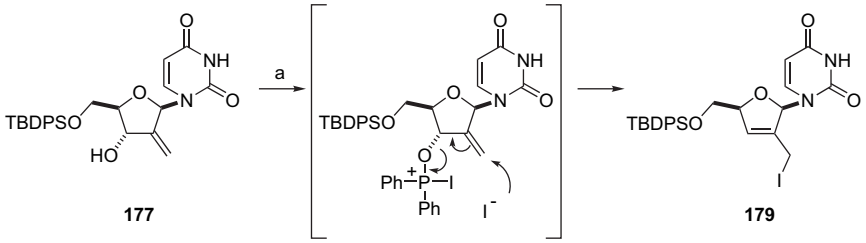
Chiacchio et al. reported a route to the 2′-*C*-methyl analogue of d4T, **195**, which employed the key steps of a 1,3-dipolar cycloaddition of a nitrone and a Cope elimination (Scheme 31).[68] The starting material, *C*-methoxycarbonyl-*C*,*N*-dimethyl nitrone (**185**), was reacted with allyl acetate to give a mixture of acetyloxymethyl derivatives **186**. Treatment of **186** with methyl triflate to give **187** and subsequent hydrogenation afforded the lactones **188** in 93% yield (three steps). Protection of the primary hydroxyl group furnished the 5′-*O*-silylated compounds **189** and **190**, which were separated by flash chromatography. Subsequent DIBALH reduction of lactone **189** proceeded with complete stereoselectivity to give, exclusively, the lactol **191** in 86% yield. After acetylation, the *N*-glycosylation of **192** with silylated thymine afforded the corresponding β-nucleoside **193**, stereoselectively, in 92% yield. Elimination of the *N*-dimethylamino group was performed according to a Cope elimination by treatment with MCPBA to form **194** followed by deprotection of the primary hydroxyl group to afford the target nucleoside **195** in 64% yield (two steps).

## 2.5. Other methods

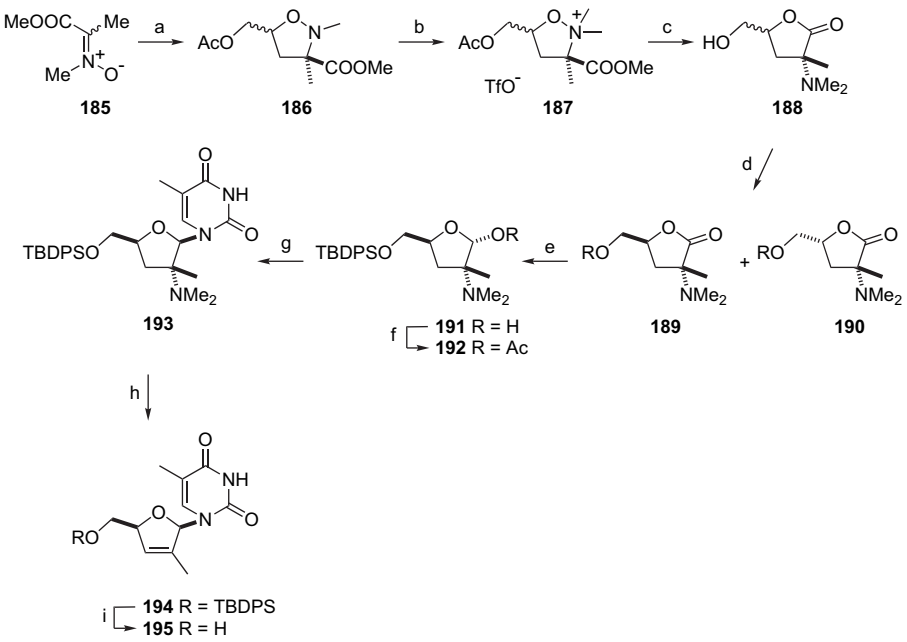
Chu et al. reported a convergent route to 2′-fluoro-2′,3′-unsaturated L-nucleosides starting from L-gulonic-γ-lactone (**196**) (Scheme 32).[69] Acetalation and cleavage of the lactone **196** afforded the L-glyceraldehyde derivative **197**, which was subjected to Horner–Emmons reaction with triethyl α-fluorophosphonoacetate and sodium bis(trimethylsilyl)amide in THF to give a mixture of olefins **198** in 98% yield. These, under acidic conditions, followed by silylation of the primary hydroxyl group, furnished the lactone **199** in 70% yield. DIBALH reduction of **199** provided the lactols **200**, which were acetylated to give the acetates **201**. *N*-Glycosylation of **201** with silylated thymine afforded the nucleoside analogues **202** and **203** and subsequent deprotection gave the target thymine analogue **150** in 26% yield (two steps) and the corresponding α-anomer **151**.



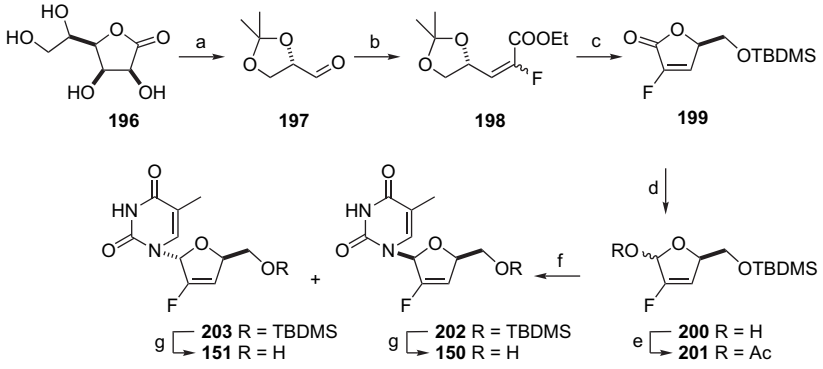

**Scheme 28**. Reagents and conditions: (a) $Ph_2PCl$, $I_2$, imidazole, toluene, MeCN (for **178**: 90%; for **179**: 90%); (b) $N(Bu)_4OAc$, $CH_2Cl_2$ (for **180**: 94%; for **181**: 96%); (c) 1. $NH_3$, MeOH; 2. TBAF, THF (for **182**: 84%; for **183**: 86%).




**Scheme 29**. Reagents and conditions: (a) $Ph_2PCl$, $I_2$, imidazole, toluene, MeCN (90%).



**Scheme 31**. Reagents and conditions: (a) AllylOAc (97%); (b) TfOMe, $CCl_4$ (100%); (c) $H_2$, Pd/C (96%); (d) TBDPSCl, imidazole, $CH_2Cl_2$ (for **189** 47%; for **190** 43%); (e) DIBALH, toluene (86%); (f) AcCl, pyridine, $CH_2Cl_2$ (88%); (g) silylated thymine, $SnCl_4$, $CH_2Cl_2$ (92%); (h) MCPBA, $CH_2Cl_2$ (65%); (i) TBAF, THF (99%).



**Scheme 32**. Reagents and conditions: (a) Ref. 70; (b) $(EtO)_2P(O)CHFCOOEt$, NaHMDS, THF (98%); (c) 1. HCl, EtOH; 2. TBDMSCl, imidazole, $CH_2Cl_2$ (70%); (d) DIBALH, $CH_2Cl_2$ (80%); (e) $Ac_2O$, $Et_3N$, $CH_2Cl_2$ (78%); (f) silylated thymine, TMSOTf, $C_2H_4Cl_2$ (64%); (g) TBAF, THF (for **150**: 41%; for **151**: 26%).

This type of strategy was also applied to extend the L-series of compounds, which included the uracil, cytosine, adenine and guanine derivatives **154** and **204**–**206**.[69] The alternative D-series **10** and **207**–**210** employed D-mannitol as the starting point (Fig. 8).[70]

Chu et al. described a second convergent route to 2′-fluoro-4′-ethynyl-2′,3′-unsaturated D- and L-nucleosides starting from the isopropylidene-protected D-glyceraldehyde **74**, which was converted in a four-step route into the lactol **211** (Scheme 33).[71] Wittig homologation of the lactol **211** and silylation of the secondary hydroxyl group furnished a 5:2 mixture of the *E*- and *Z*-dienes **212** and **213**, respectively, in 80% total yield, which were separated by chromatography. The *E*-isomer **212** was converted into the diol **214** in 83% yield using the classical oxidation reagents $OsO_4$ and NMO. Selective benzoylation of the primary hydroxyl group afforded the ester **215** and subsequent oxidation by pyridinium chlorochromate gave the α,β-unsaturated ketone **216**, which is the key intermediate in the strategy, since it is universal for routes to both the D- and L-series of nucleosides. A Grignard reaction of **216** with HCCMgBr gave a separable mixture of the two tertiary alcohols **217** and **218**, in a ratio of 3:2, respectively, with a total yield of 72%. To obtain compounds in the D-series, the TBDMS groups of one of the alcohols **217** were removed with TBAF to form **219**, followed by periodate oxidation and acetylation with acetic anhydride to give the 3-fluoro-2,3-unsaturated-4-ethynyl-D-furanose **220** in 76% yield (three steps). *N*-Glycosidation of **220** with silylated thymine afforded the nucleoside **221** in 55% yield and the corresponding anomer **222** in 18% yield. Subsequent deprotection of the primary hydroxyl group of **221** furnished the target nucleoside **223** in 91% yield.

The same strategy was applied to extending the D-series of compounds to include the cytosine and adenine derivatives **224** and **225**. The alternative L-series **226**–**228** employed the alcohol **218** obtained from the ketone branch point intermediate **216** in the strategy (Fig. 9).

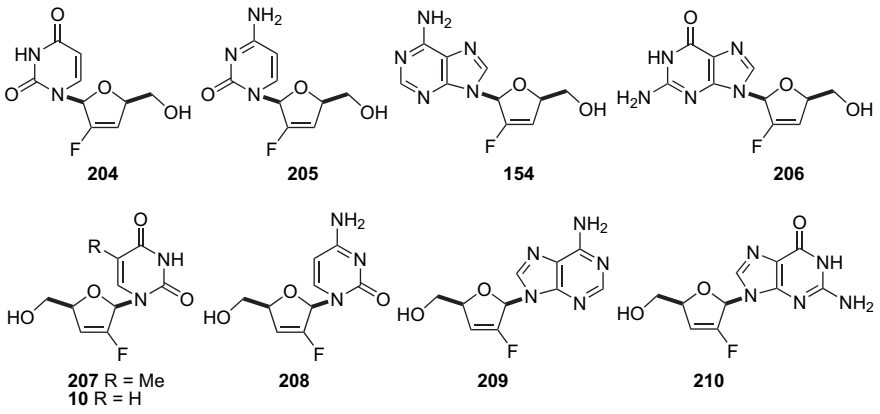
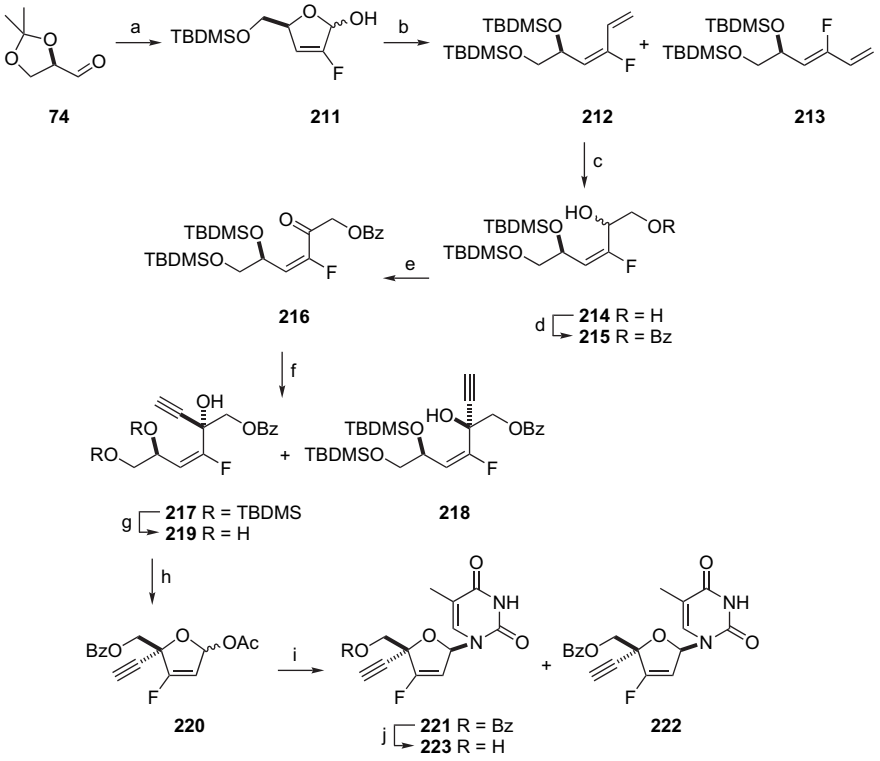



**Figure 8**. 2′-Fluoro nucleosides **10**, **154** and **204**–**210**.




**Scheme 33**. Reagents and conditions: (a) 1. $(EtO)_2P(O)CHFCOOEt$, NaHMDS, THF (98%), 2. HCl, EtOH; 3. TBDMSCl, imidazole, $CH_2Cl_2$ (70%); 4. DIBAHL, $CH_2Cl_2$ (80%); (b) 1. $MePPh_3Br$, NaH, DMSO, THF (91%); 2. TBDMSCl, imidazole, $CH_2Cl_2$ (87%); (c) $OsO_4$, NMO, acetone, $H_2O$ (83%); (d) BzCl, pyridine (84%); (e) PCC, 4 Å molecular sieves, $CH_2Cl_2$ (72%); (f) HCCMgBr, THF (72%); (g) TBAF, AcOH, THF (98%); (h) 1. $NaIO_4$, EtOH, $H_2O$; 2. $Ac_2O$, pyridine (78%); (i) silylated thymine, $SnCl_4$, $C_2H_4Cl_2$ (10%); (j) $NH_3$, MeOH (91%).

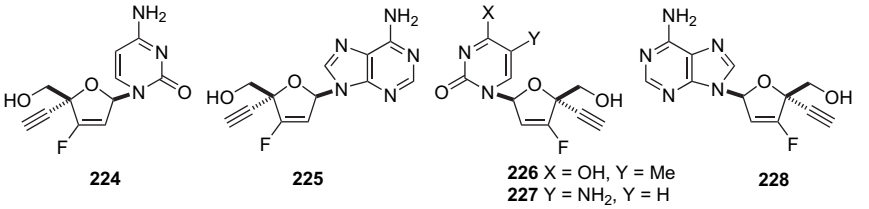
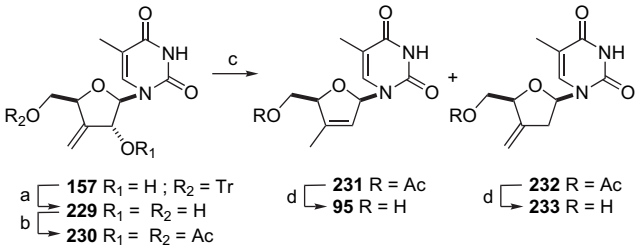



**Figure 9**. 4′-Ethynyl-2′-fluoro nucleosides **224**–**228**.

Allylic acetates are known to be converted into the corresponding olefins using organopalladium chemistry. Application of this methodology to nucleoside chemistry was explored by Matsuda et al.[63] Detritylation of the methylidene nucleoside **157** afforded **229**, followed by acetylation, furnished the diacetate **230** in 88% yield (two steps), which was reduced with $LiBH_4$ in the presence of $PPh_3$ and a catalytic amount of $(PhCN)_2PdCl_2$ in THF to give a mixture of

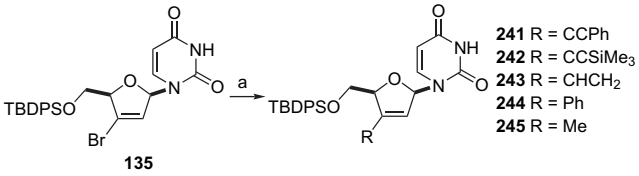
**231** and **232** (3:1) in 50% yield. Classical chromatographic purification and deprotection of the primary hydroxyl group in each case gave the 3′-methyl derivative **95** and the *exo* olefin **233** in 98% and 95% yield, respectively (Scheme 34).




**Scheme 34**. Reagents and conditions: (a) HCOOH (97%); (b) $Ac_2O$, DMAP, MeCN (89%); (c) $LiBH_4$, $PPh_3$, $(PhCN)_2PdCl_2$ (50%); (d) MeONa, MeOH (for **95**: 98%; for **233**: 95%).

In 1993, Chattopadhyaya et al. reported evidence for nitroxide radical formation in a radical-promoted denitration reaction, as part of a study to synthesise various 3′-branched 2′,3′-unsaturated nucleosides, as exemplified by the synthesis of **240** (Scheme 35).[72] Thus, the thymidine analogue **234** was treated with *N*-methylhydroxylamine hydrochloride in pyridine to give the corresponding 3′-(*E*)-methylnitrone **235** in 52% yield. This was treated with ethyl vinyl ether and acrylonitrile to afford the 3′-spiro nucleoside **236** by 1,3-dipolar cycloaddition. Desilylation to give **237** and deoxygenation of the secondary hydroxyl group vicinal to the 3′-spiro function via **238** gave the 3′-*C*-substituted nucleoside **239**, which was deprotected to furnish the target compound **240** in 18% yield (four steps).

Various 2′- and 3′-*C*-branched 2′,3′-unsaturated nucleosides were prepared starting from 2′,3′-didehydro-2′,3′-dideoxynucleosides. Tanaka et al. described the synthesis of 2′-*C*- and 3′-*C*-branched 2′,3′-unsaturated nucleosides via palladium-catalysed cross-coupling of the bromovinyl intermediates.[59,60] The 3′-bromo derivative **135** was subjected to a Sonogashira reaction, which gave the nucleosides **241** and **242** (Scheme 35) and, in the same paper, Tanaka et al.[60] described an alternative method using organotin reagents, as coupling partners, to obtain the nucleosides **243–245** (Scheme 36).



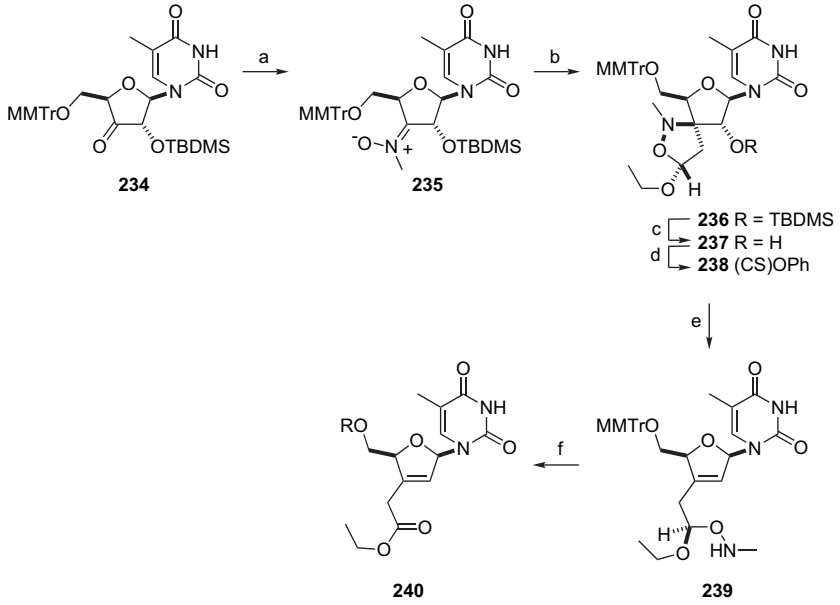

**Scheme 36**. Reagents and conditions: (a) For **241**: PhCCH, $(Ph_3P)_2PdCl_2$/CuI, $Et_3N$, DMF (68%); for **242**: $Me_3SiCCH$, $(Ph_3P)_2PdCl_2$/CuI, $Et_3N$, DMF (62%); for **243**: $Bu_3SnCHCH_2$, $(Ph_3P)_2PdCl_2$/CuI, $Et_3N$, DMF (37%); for **244**: $Ph_4Sn$, $(Ph_3P)_2PdCl_2$/CuI, dioxane (39%); for **245**: $Me_4Sn$, $(Ph_3P)_4Pd$, dioxane (14%).

In a similar manner, 2′-*C*- and 3′-*C*-bromovinyl nucleosides **136–138** were subjected to the Sonogashira cross-coupling reaction to afford the corresponding nucleosides **246–254** (Fig. 10).

Tanaka et al. reported the vinylic stannylation of d4T at either the 3′- or 2′-position using $Bu_3SnOMe$ followed by TMEDA, LTMP and HMPA.[73] Thus, the 3′-*C*-stannyl derivative **255** was obtained in 60% yield. Application of organotin chemistry at the Sn–C bond of the nucleoside **255** provided access to a variety of 3′-substituted d4T analogues (**256–261**) in 73–100% yield (Scheme 37).

Using a similar procedure, Tanaka et al. reported the synthesis of various 3′-*C*-branched analogues **262–266** (Fig. 11).[56]

2′-*C*-Vinyl- and 3′-*C*-vinyl-2′,3′-unsaturated nucleosides were obtained starting from different monosaccharides. Schmalz et al. reported the synthesis of 3′-*C*-vinyl d4Ns




**Scheme 35**. Reagents and conditions: (a) MeNHOH, pyridine (52%); (b) ethyl vinyl ether (94%); (c) $NH_4F$, MeOH (93%); (d) PhO(CS)Cl, DMAP, MeCN (85%); (e) $Bu_3SnH$, AIBN, toluene (30%); (f) AcOH, $H_2O$ (75%).

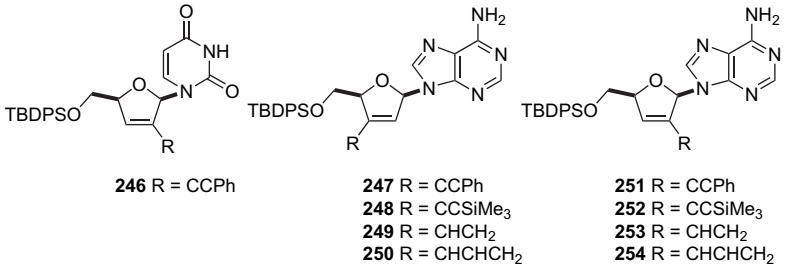
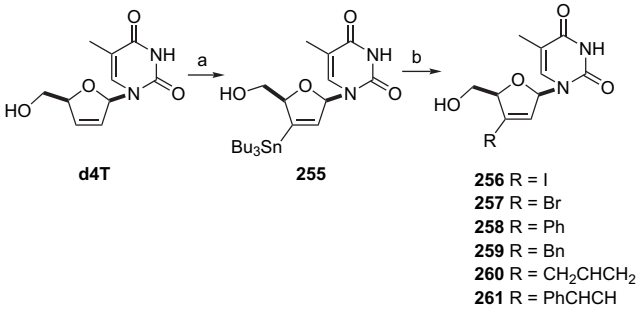



**Figure 10**. 2′- and 3′-*C*-Branched nucleosides **246**–**254**.




**Scheme 37**. Reagents and conditions: (a) 1. $Bu_3SnOMe$; 2. LTMP, HMPA, TMEDA, THF (60% two steps); (b) for **256**: $I_2$, THF (93%); for **257**: NBS, THF (100%); for **258**: PhI, $(PPh_3)_4Pd$, CuI, DMF (97%); for **259**: BnBr, $(PPh_3)_4Pd$, CuI, DMF (78%); for **260**: AllBr, $(PPh_3)_4Pd$, CuI, DMF (73%); for **261**: β-bromostyrene, $(PPh_3)_4Pd$, CuI, DMF (81%).

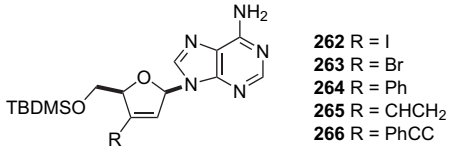


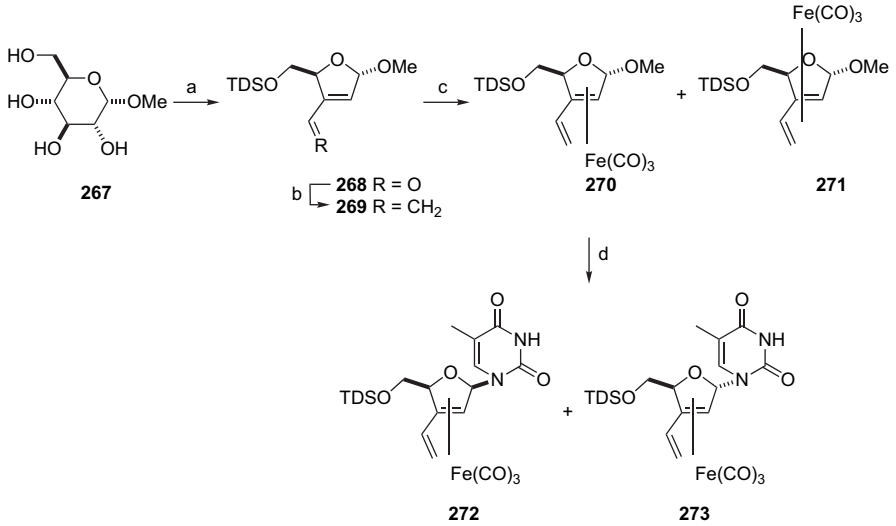

**Figure 11**. 3′-*C*-Branched adenosine derivatives **262**–**266**.

starting from methyl α-D-glucopyranoside (**267**)[74] in which it was first converted into the aldehyde **268** by a sequence of reactions involving selective silylation of the primary hydroxyl group, Mitsunobu epoxidation and LiBr-induced rearrangement/ring contraction. Wittig homologation of **268** and, finally, diastereoselective complexation of the diene **269** with $[Fe_2(CO)_9]$ gave a mixture of the *endo*-complexes **270** and **271** (3.3:1). The major product **270** was subjected to *N*-glycosidation using Vorbruggen chemistry to furnish the protected anomeric pair of nucleosides **272** and **273** (1.6:1) in 27% total yield (Scheme 38).

Application of this strategy also permitted the synthesis of the corresponding 3′-*C*-vinyl nucleosides **274**–**287** (Fig. 12).

Schmalz et al. reported the synthesis of 2′-*C*-vinyl-2′,3′-unsaturated nucleosides starting from D-ribonolactone (**288**).[74] After selective tritylation, the lactone **288** was converted into the enol triflate **289** in 85% yield. Then, C–C bond formation was achieved via Stille coupling using tributylvinylstannane to afford the diene **290** in 87% yield. Complexation of the 1,3-butadiene derivative **290** with $[Fe_2(CO)_9]$ gave a mixture of complexes **291** and **292**, which was readily separated by flash chromatography. Subsequent reduction of **291** with DIBAHL, acidic methanolysis and silylation furnished the corresponding diene **293** in 87% yield. Diastereoselective *N*-glycosidation provided the target β-nucleoside **294**, stereoselectively, in 22% overall yield (Scheme 39).

Application of this procedure for different heterocyclic bases afforded the nucleosides **295**–**300** (Fig. 13).




**Scheme 38**. Reagents and conditions: (a) 1. TDSCl, pyridine (98%); 2. DEAD, $PPh_3$, benzene (81%); 3. LiBr, $(Me_2N)_2CO$, toluene (68%); (b) $CH_2PPh_3$, THF (86%); (c) $[Fe_2(CO)_9]$, $Et_2O$ (72%); (d) silylated thymine, $SnCl_4$, $C_2H_4Cl_2$ (82%).

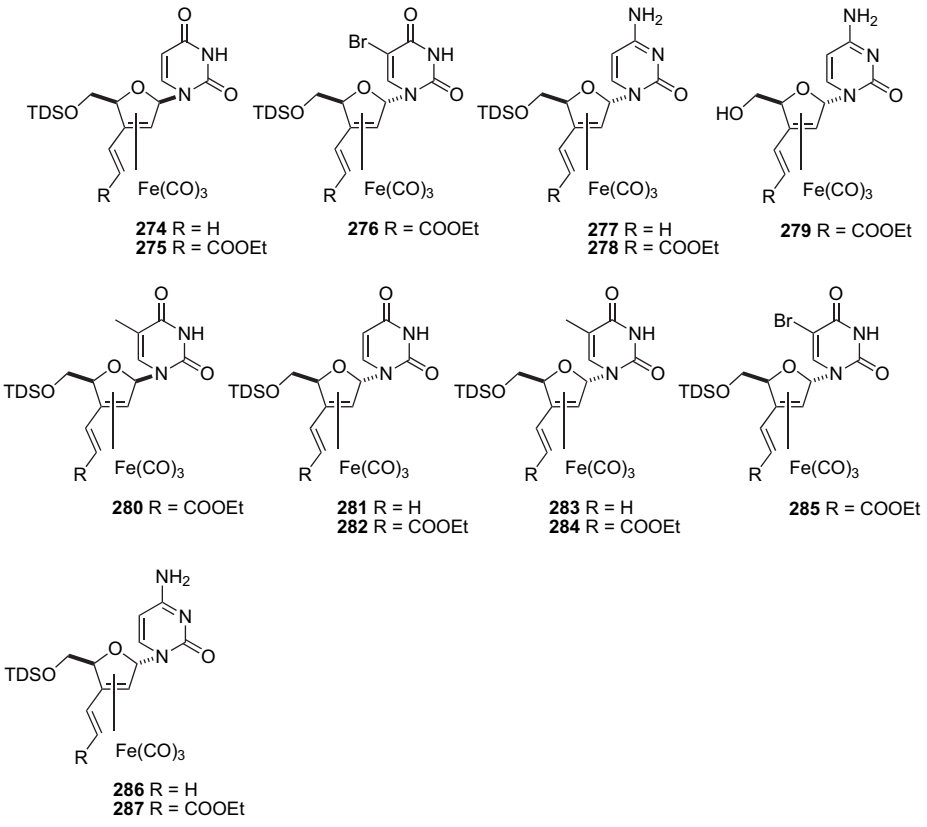
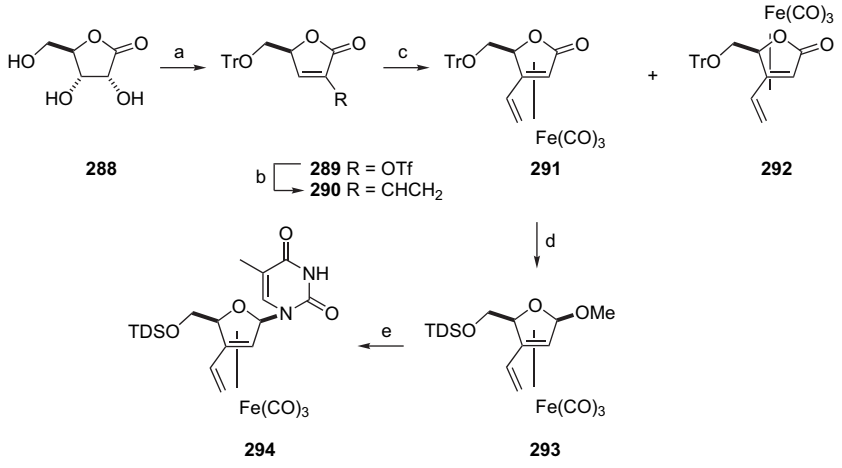



**Figure 12**. 3′-*C*-Vinyl nucleoside derivatives **274**–**287**.




**Scheme 39**. Reagents and conditions: (a) 1. TrCl, pyridine (67%); 2. $Tf_2O$, pyridine, $CH_2Cl_2$ (85%); (b) $Bu_3SnCHCH_2$, $Ph_3As$, $[Pd_2(dba)_3]$, LiCl, THF (87%); (c) $[Fe_2(CO)_9]$, EtOAc (69%); (d) 1. DIBAHL, toluene (92%); 2. $HC(OMe)_3$, PTSA, MeOH (99%); TDSCl, imidazole, $CH_2Cl_2$ (96%); (e) silylated thymine, $SnCl_4$, $C_2H_4Cl_2$ (75%).

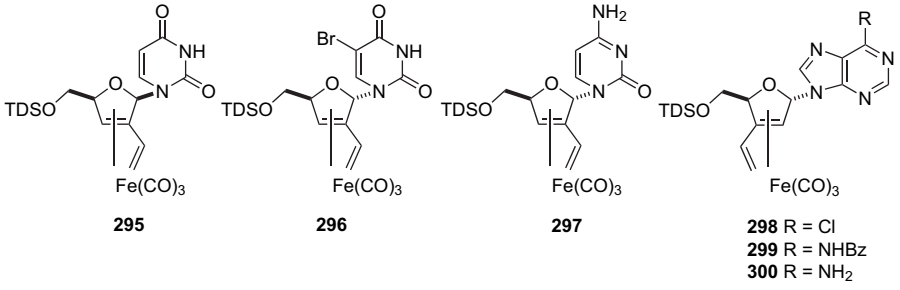



**Figure 13**. 2′-*C*-Vinyl nucleoside derivatives **295**–**300**.

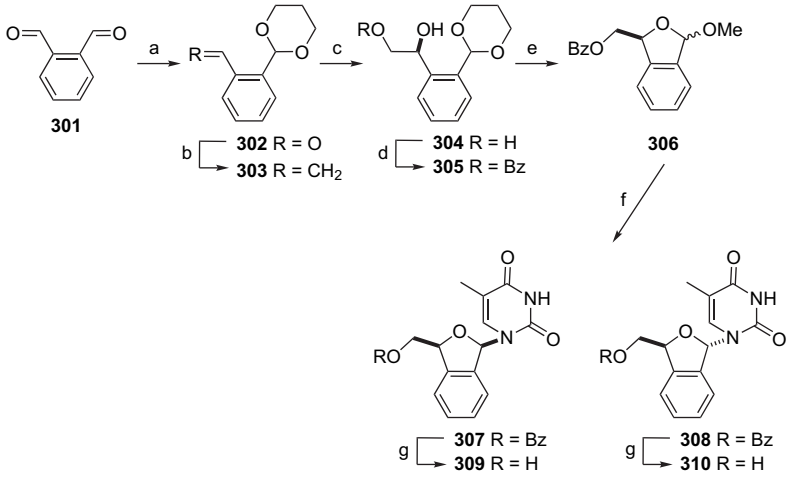
## 3. Synthesis of 2′- and 3′-dibranched 2′,3′-unsaturated nucleosides

Analogues of d4T having a benzo[*c*]furan core were described by Ewing et al.[75–81] The target nucleosides were first obtained as a racemic mixture[75] and, in subsequent papers, as enantiomerically pure forms.[76–81] For simplicity, only the asymmetric synthesis of benzo[*c*]furan analogues are described here. Starting from phthalaldehyde **301**, selective protection of one of the formyl groups was achieved by acetal formation to give **302**. This was followed by Wittig homologation of the remaining formyl group to give the corresponding styrene **303** in 58% yield. The ethene functional group was converted into the corresponding dihydro derivatives **304** in 85% yield (ee>99%) using the commercial Sharpless reagent, AD-mix α. After selective benzoylation of the primary hydroxyl group of **304**, the corresponding esters **305** were cyclised and methylated to afford the corresponding 1,3-dihydrobenzo[*c*]furan derivatives **306** in 82% yield (two steps), analogous to an anomeric mixture of 2′,3′-didehydro-2′,3′-dideoxyfuranosides. Both of the thymine derivatives **307** and **308** were obtained by standard Vorbruggen chemistry on **306**, due to the lack of neighbouring group participation to direct stereoselectivity. After removal of the benzoyl protection and subsequent silica gel chromatography, the target nucleosides **309** and **310** were obtained enantiomerically pure in 9% and 19% overall yield, respectively (Scheme 40).

The nucleosides **309** and **310** are analogous to 2′,3′-didehydro-2′,3′-dideoxynucleosides in the D-series. The related enantiomers analogous to L-nucleosides were synthesised using the same strategy, but employing AD-mix β. This work was further extended to provide the full set of related isomers **311**–**315**, having uracil and cytosine as heterocyclic bases, accordingly (Fig. 14). In each case, the use of the appropriate AD-mix afforded an enantiomerically pure nucleoside.[76]

## 4. Conclusions

A major initiative to synthesise 2′,3′-didehydro-2′,3′-dideoxynucleosides branched at the olefinic moiety has been led by attempts to discover compounds with increased activity over d4T, to provide structure–activity data and to offer a continuity of new drugs as alternatives to the previous generation to combat the rise of resistance. To date, the majority of work has been directed towards 2′,3′-didehydro-2′,3′-dideoxynucleosides having branching at either the 2′- or 3′-positions. Although most examples in this field are pyrimidine nucleosides, the corresponding purine analogues have also received some attention. Not surprisingly, however, most targets have been closely related to d4T, with the fluorine-branched analogues perhaps being the most commonly sought by a number of research groups, resulting in an interesting and diverse number of strategies having been explored.[28,29,35,36,44–48,62,69–71] The other halogens, chlorine,[37,38] bromine[56,59,60,73] and iodine,[56,73] have also received some attention along with the azide.[37,38] After fluorine as a substituent, however, the next most attractive targets have been nucleosides with a branched methyl group




**Scheme 40**. Reagents and conditions: (a) propan-1,3-diol, PTSA, toluene (75%); (b) $Ph_3PMe$, BuLi, THF (77%); (c) AD-mix α, *t*-BuOH, $H_2O$ (85%); (d) BzCl, pyridine (89%); (e) HCl, MeOH (92%); (f) silylated thymine, TMSOTf, $C_2H_4Cl_2$ (for **307**: 23%; for **308**: 47%); (g) $NH_3$, MeOH (quant).

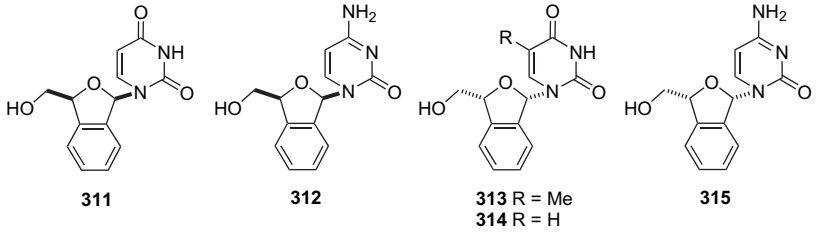



**Figure 14**. 2′-*C*- and 3′-*C*-Dibranched nucleosides **311**–**315** having a benzo[*c*]furan core.

or an analogous alkyl substituent[39–41,50,59,60,63,64,66–68,74] and, to a lesser extent, a nitrile group.[42,43,49,51–55] Such targets have also been obtained by diverse strategies. Other functional groups attached to the olefinic part of such nucleosides include, stannyl,[56,73] thio,[56] seleno,[58] phenyl,[73] alkynyl[56,59,60] and, to a greater extent, alkenyl.[56,59,60,73] More recently, the latter type has attracted attention in the form of $Fe(CO)_3$ complexes of 2′-*C*-vinyl- and 3′-*C*-vinyl-2′,3′-unsaturated nucleosides.[74] A novel type of 2′,3′-didehydro-2′,3′-dideoxynucleoside which is analogous to d4T, but where the unsaturation at the 2′,3′-positions is part of a benzo[*c*]furan system has been observed.[75–81] Such types of nucleoside analogues form the sole examples of 2′,3′-didehydro-2′,3′-dideoxynucleosides, which can be classified as having branching at both the 2′- and 3′-positions. Thus, routes to such compounds have required alternative approaches to those of other 2′,3′-didehydro-2′,3′-dideoxynucleoside, at least in constructing the glycone-type moiety.

Most of the strategies employed to obtain 2′,3′-didehydro-2′,3′-dideoxynucleosides branched at the olefinic group of the glycone have depended upon total rather than partial synthesis (i.e., modification of naturally occurring nucleosides). In most cases, total synthesis has involved in a convergent approach, where the glycone moiety is constructed with the required branching group in place before, or introduced after, attachment of the heterocyclic base, and where the olefinic group is formed in the final step prior to deprotection. To date, there are only a few examples[62,69,71,74,76–81] of convergent syntheses in which the final target functionalities in the 2′- and/or 3′-positions and π-character are present on the glycone precursor immediately prior to condensation to effect nucleoside formation. Classical chemistry has played a major role involving base (e.g., NaOH, *t*-BuOK, MeONa and, sometimes, DBN) catalysis to effect the elimination step and with nucleofuges such as *O*-2,3′-anhydro systems, F and OMs with the latter proving to be the most popular.[28,29,35–58] Eliminations have included those in which the leaving group is on the 2′-position and eventual branching is on the 3′-position or vice versa. An alternative popular approach has used ketonic carbonyls on either the 2′- or 3′-positions, which have facilitated both a branching group and leaving group on the same carbon, as in the example of *gem* difluoro derivatives giving fluoro-branched olefins.[44,46–48] Both base-catalysed cis- and trans-elimination reactions have proved successful. The latter have been used where the nucleofuge is substituted either α or β to the branching group, whereas the former have been limited to cases where the nucleofuge is β to the branch. cis-Eliminations have included classical-type base-catalysed eliminations, but also intramolecular base catalysis is involved with participation from a thiocarbonyl group. Base-catalysed eliminations have provided a reasonably diverse set of branching groups to include F, Cl, $N_3$, Me, $CF_3$, CN, PhS, $SO_2Ph$, $SnBu_3$, SePh and $SeO_2Ph$. Oxidative eliminations [59–62] have been used to a lesser extent in which the double bond is generated by oxidation of PhSe with MCPBA. Both total and divergent routes have been used to obtain the PhSe-substituted nucleosides. Such oxidations have, however, been limited to introducing the halogens F, Cl and Br in either the 2′- or 3′-positions of the olefinic nucleosides. The introduction of methyl or methylene groups in such nucleosides has made good use of the hetero-Cope reaction.[63–67] Although routes to nucleosides using this chemistry are multistep, the yields are quite high. Some examples have involved an efficient intramolecular addition–elimination mechanism with either oxalate or imidazole thiocarbonyl groups followed by high-yielding radical deoxygenation or desulfurisation, by Barton-type chemistry, and subsequent rearrangement of an exocyclic double bond to give a methyl group at either of the 2′- or 3′-positions. Variations which involve intermolecular introduction of a function group at the exocyclic double bond have also been successful using nucleophiles such as azide or iodide and have generated nucleosides with, e.g., $CH_2N_3$, $CH_2OH$ or $CH_2I$, in either the 2′- or 3′-positions.[65–67] Another rearrangement has been that of an exocyclic double bond, in the form of an allylic acetate nucleoside derivative, to form the target system employing organopalladium chemistry.[59,60] Worthy of mention is an individual approach involving the construction of the glycone moiety by a 1,3-cycloaddtion reaction and eventual Cope elimination of an *N*-dimethylamino group to obtain a methyl group in the 2′-position.[68] An interesting example of how to introduce a fluoro-substituted alkene into a nucleoside has involved a Horner–Emmons reaction at an early synthetic step and eventually constructing the glycone moiety with the required functionality ready for attachment of the base.[69] This strategy has been exploited to produce a number of purine and pyrimidine 2′- and 3′-fluoro derivatives. An individual approach was to form the 3′-spiro nucleoside **236** via a 1,3-dipolar addition and ring open to form an ethoxycarbonylmethylene branch at the 3′-position.[72] A more general approach has been the direct substitution of 2′,3′-didehydro-2′,3′-dideoxynucleosides to introduce branch groups at either the 2′- or 3′-positions by coupling bromovinyl nucleosides[59,60] with organopalladium and organotin reagents or, alternatively, by forming a tertiary butyltin vinyl nucleoside and palladium-catalysed cross-coupling.[56,73] These methods have conveniently provided a variety of branch groups in the 2′- or 3′-positions including phenyl, alkyl, alkenyl, alkynyl and halogens. Additionally convenient in accessing a variety of derivatives has been the direct coupling to d4T by stannylation at the 2′-position and subsequent halogenation or palladium-assisted carbon–carbon coupling with a variety of aryl, alkyl and alkenyl groups. 2′-Alkenyl derivatives as $Fe(CO)_3$ complexes have been approached by an alternative route of constructing a 2′-*C*-vinylic glycone moiety, complexing it with $Fe(CO)_3$ and then condensing with a pyrimidine base.[74] This methodology was extended to the 3′-*C*-vinylic series with different pyrimidine bases. Finally, a series of 2′-*C*- and 3′-*C*-dibranched nucleosides with a benzo[*c*]furan core have been synthesised by a convergent route employing conventional Vorbruggen chemistry on a preformed benzo[*c*]furan system.[75–81] An interesting feature of the route to this unusual glycone system in nucleoside chemistry is the highly effective use of the stereoselective Sharpless hydroxylation to obtain compounds analogous to conventional nucleosides in the D- and L-series, accordingly.

## References and notes

1. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096–7100.

2. Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1987**, *30*, 1270–1278.
3. Daluge, S. M.; Purifoy, D. J.; Savina, P. M.; St Clair, M. H.; Parry, N. R.; Dev, I. K.; Novak, P.; Ayers, K. M.; Reardon, J. E.; Roberts, G. B.; Fyfe, J. A.; Blum, M. R.; Averett, D. R.; Dornsife, R. E.; Domin, B. A.; Ferone, R.; Lewis, D. A.; Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1994**, *38*, 1590–1603.
4. Larder, B. A.; Kemp, S. D.; Harrigan, P. R. *Science* **1995**, *269*, 696–699.
5. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911–1915.
6. Chu, C. K.; Schinazi, R. F.; Arnold, B. H.; Cannon, D. L.; Doboszewski, B.; Bhadti, V. B.; Gu, Z. *Biochem. Pharmacol.* **1988**, *37*, 3543–3548.
7. De Clercq, E.; Van Aerschot, A.; Herdewijn, P.; Baba, M.; Pauwels, R.; Balzarini, J. *Nucleosides Nucleotides* **1989**, *8*, 659–671.
8. Schinazi, R. F.; Sommadossi, J. P.; Saalmann, V.; Cannon, D. L.; Xie, M. Y.; Hart, G. C.; Smith, G. A.; Hahn, E. F. *Antimicrob. Agents Chemother.* **1990**, *34*, 1061–1067.
9. Coates, J. A. V.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202–205.
10. Schinazi, R. F.; Lloyd, R. M.; Nguyen, M. N.; Cannon, D. L.; Mcmillan, A.; Ilksoy, N.; Chu, C. K.; Liotta, D. C.; Bazmi, H. Z.; Mellors, J. W. *Antimicrob. Agents Chemother.* **1993**, *37*, 875–881.
11. Rousseau, F. S.; Kahn, J. O.; Thompson, M.; Mildvan, D.; Shepp, D.; Sommadossi, J. P.; Delehanty, J.; Simpson, J. N.; Wang, L. H.; Quinn, J. B.; Wakeford, C.; van der Horst, C. *J. Antimicrob. Chemother.* **2001**, *48*, 507–513.
12. Molina, J. M.; Ferchal, F.; Rancinan, C.; Raffi, F.; Rozenbaum, W.; Sereni, D.; Morlat, P.; Journot, V.; Decazes, J. M.; Chene, G. *J. Infect. Dis.* **2000**, *182*, 599–602.
13. Lin, T. S.; Schinazi, R. F.; Prusoff, W. H. *Biochem. Pharmacol.* **1987**, *36*, 2713–2718.
14. Balzarini, J.; Van Aerschot, A.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1989**, *38*, 869–874.
15. Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; St Clair, M. H. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082–1093.
16. Tisdale, M.; Alnadaf, T.; Cousens, D. *Antimicrob. Agents Chemother.* **1997**, *41*, 1094–1098.
17. Faletto, M. B.; Miller, W. H.; Garvey, E. P.; St Clair, M. H.; Daluge, S. M. *Antimicrob. Agents Chemother.* **1997**, *41*, 1099–1107.
18. Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. *Antiviral Chem. Chemother.* **1997**, *8*, 557–564.
19. Robbins, B. L.; Srinivas, R. V.; Kim, C.; Bischofberger, N.; Fridland, A. *Antimicrob. Agents Chemother.* **1998**, *42*, 612–617.
20. Bolon, P. J.; Wang, P.; Chu, C. K.; Gosselin, G.; Boudou, V.; Pierra, C.; Mathé, C.; Imbach, J. L.; Faraj, A.; Abdelaziz El Alaoui, M.; Sommadossi, J. P.; Balakrishna Pai, S.; Zhu, Y. L.; Lin, J. S.; Cheng, T. C.; Schinazi, R. F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1657–1662.
21. Lin, T. S.; Luo, M. Z.; Liu, M. C.; Zhu, Y. L.; Gullen, E.; Dutschman, G. E.; Cheng, Y. C. *J. Med. Chem.* **1996**, *39*, 1757–1759.
22. Herdewijn, P.; Pauwels, R.; Baba, M.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 2131–2137.
23. Balzarini, J.; Pauwels, R.; Baba, M.; Robins, M. J.; Zou, R.; Herdewijn, P.; De Clercq, E. *Biochem. Biophys. Res. Commun.* **1987**, *145*, 269–276.
24. Shi, J.; Mcatee, J. J.; Schlueter-Wirtz, S.; Tharnisch, P.; Juodawlkis, A.; Liotta, D. C.; Schinazi, R. F. *J. Med. Chem.* **1999**, *42*, 859–867.
25. Ma, L.; Hurwitz, S. J.; Shi, J. X.; Mcatee, J. J.; Liotta, D. C.; Mcclure, H. M.; Schinazi, R. F. *Antimicrob. Agents Chemother.* **1999**, *43*, 381–384.
26. Baba, M.; Pauwels, R.; Balzarini, J.; Herdewijn, P.; De Clercq, E. *Biochem. Biophys. Res. Commun.* **1987**, *145*, 1080–1086.
27. Herdewijn, P.; Balzarini, J.; Baba, M.; Pauwels, R.; Van Aerschot, A.; Janssen, G.; De Clercq, E. *J. Med. Chem.* **1988**, *31*, 2040–2048.
28. Martin, J. A.; Busshnell, D. J.; Duncan, I. B.; Dunsdon, S. J.; Hall, M. J.; Machin, P. J.; Merrett, J. H.; Parkes, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A. *J. Med. Chem.* **1990**, *33*, 2137–2145.
29. Tann, C. H.; Brodfueher, P. R.; Brundidge, S. P.; Sapino, C.; Howell, H. G. *J. Org. Chem.* **1985**, *50*, 3644–3647.
30. Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M. *Tetrahedron Lett.* **1964**, *38*, 2725–2727.
31. Horwitz, J. P.; Chua, J.; Klundt, I. L.; Da Rooge, M. A.; Noel, M. *J. Am. Chem. Soc.* **1964**, *86*, 1896–1897.
32. Horwitz, J. P.; Chua, J. *Synthetic Procedures in Nucleic Acid Chemistry*; Zobrach, W. W., Tipson, R. S., Eds.; Interscience: New York, NY, 1968; Vol. 1, p 344.
33. Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205–211.
34. Horwitz, J. P.; Chua, J.; Noel, M.; Donatti, J. T. *J. Org. Chem.* **1967**, *32*, 817–818.
35. Sterzycki, R. Z.; Ghazzouli, I.; Brankovan, V.; Martin, J. C.; Mansuri, M. M. *J. Med. Chem.* **1990**, *33*, 2150–2157.
36. Huang, J. T.; Chen, L. C.; Wang, L.; Kim, M. H.; Warshaw, J. A.; Armastrong, D.; Zhu, Q. Y.; Chou, T. C.; Watanabe, K. A.; Matulic-Adamic, J.; Su, T. S.; Fox, J. J.; Polsky, B.; Baron, P. A.; Gold, J. W. M.; Hardy, W. D.; Zuckerman, E. *J. Med. Chem.* **1991**, *34*, 1640–1646.
37. Mikhailopoulo, I. A.; Pricota, T. I.; Sivets, G. G.; Altona, C. *J. Org. Chem.* **2003**, *68*, 5897–5908.
38. Mikhailopoulo, I. A.; Poopeiko, N. E.; Pricota, T. I.; Sivets, G. G.; Kvasyuk, E. I.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1991**, *34*, 2195–2202.
39. Lavaire, S.; Plantier-Royon, R.; Portella, C.; De Monte, M.; Kirn, A.; Aubertin, A. M. *Nucleosides Nucleotides* **1998**, *17*, 2267–2280.
40. Lavaire, S.; Plantier-Royon, R.; Portella, C. *J. Carbohydr. Chem.* **1996**, *15*, 361–370.
41. Jeannot, F.; Gosselin, G.; Standring, D.; Bryant, M.; Sommadossi, J. P.; Loi, A. G.; La Colla, P.; Mathé, C. *Bioorg. Med. Chem.* **2002**, *10*, 3153–3161.
42. Zhu, W.; Gumina, G.; Schinazi, R. F.; Chu, C. K. *Tetrahedron* **2003**, *59*, 6423–6431.
43. Filichev, V. V.; Brandt, M.; Pedersen, E. B. *Carbohydr. Res.* **2001**, *333*, 115–122.
44. Van Aerschot, A.; Herdewijn, P.; Balzarini, J.; Pauwels, R.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 1743–1749.
45. Bergstrom, D.; Romo, E.; Shum, P. *Nucleosides Nucleotides* **1987**, *6*, 53–61.
46. Chong, Y.; Gumina, G.; Mathew, J. S.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2003**, *46*, 3245–3256.
47. Gumina, G.; Schinazi, R. F.; Chu, C. K. *Org. Lett.* **2001**, *3*, 4177–4180.

48. Zhou, W.; Gumina, G.; Chong, Y.; Wang, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2004**, *47*, 3399–3408.
49. Wu, J. C.; Chattopadhyaya, J. *Tetrahedron* **1989**, *45*, 855–862.
50. Fedorov, I. I.; Kazmina, E. M.; Novicov, N. A.; Gurskaya, G. V.; Bochkarev, A. V.; Kasko, M. V.; Victorova, L. S.; Kukhanova, M. K.; Balzarini, J.; De Clercq, E.; Krayevski, A. A. *J. Med. Chem.* **1992**, *35*, 4567–4575.
51. Matsuda, A.; Nakajima, Y.; Azuma, A.; Tanaka, M.; Sasaki, T. *J. Med. Chem.* **1991**, *34*, 2917–2919.
52. Azuma, A.; Nakajima, Y.; Nishizono, N.; Minakawa, N.; Suzuki, M.; Hanaoka, K.; Kobayashi, T.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Med. Chem.* **1993**, *36*, 4183–4189.
53. Calvo-Mateo, A.; Camarasa, M. J.; Diaz-Ortiz, A.; De Las Heras, F. G.; Alemany, A. *Tetrahedron* **1988**, *44*, 4895–4903.
54. Matsuda, A.; Satoh, M.; Nakashima, H.; Yamamoto, N.; Ueda, T. *Heterocycles* **1988**, *27*, 2545–2548.
55. Faul, M. M.; Huff, B. E.; Dunlap, S. E.; Frank, S. A.; Fritz, J. E.; Kaldor, S. W.; Le Tourneau, M. E.; Stazak, M. A.; Ward, J. A.; Werner, J. A.; Winneroski, L. L. *Tetrahedron* **1997**, *53*, 8085–8104.
56. Onuma, S.; Kumamoto, H.; Kawato, M.; Tanaka, H. *Tetrahedron* **2002**, *58*, 2497–2503.
57. Wu, J. C.; Pathak, T.; Tong, W.; Vial, J. M.; Remaud, G.; Chattopadhyaya, J. *Tetrahedron* **1988**, *44*, 6705–6722.
58. Wu, J. C.; Chatoopadhyaya, J. *Tetrahedron* **1989**, *45*, 4507–4522.
59. Haraguchi, K.; Itoh, Y.; Tanaka, H.; Miyasaka, T. *Tetrahedron Lett.* **1991**, *32*, 3391–3394.
60. Haraguchi, K.; Itoh, Y.; Tanaka, H.; Akita, M.; Miyasaka, T. *Tetrahedron* **1993**, *49*, 1371–1390.
61. Haraguchi, K.; Tanaka, H.; Itoh, Y.; Miyasaka, T. *Tetrahedron Lett.* **1991**, *32*, 777–780.
62. Chen, S. H.; Wang, Q.; Mao, J.; King, I.; Dutschman, G. E.; Gullen, E. A.; Cheng, Y. C.; Doyle, T. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1589–1594.
63. Matsuda, A.; Okajima, H.; Ueda, T. *Heterocycles* **1989**, *29*, 25–28.
64. Czernecki, S.; Ezzitouni, A.; Krausz, P. *Synthesis* **1990**, 651–653.
65. Czernecki, S.; Ezzitouni, A. *J. Org. Chem.* **1992**, *57*, 7325–7328.
66. Czernecki, S.; Ezzitouni, A. *Tetrahedron Lett.* **1993**, *34*, 315–318.
67. Ionnidis, P.; Classon, B.; Samuelsson, B.; Kvarnstrom, I. *Nucleosides Nucleotides* **1993**, *12*, 449–462.
68. Chiacchio, U.; Rescifina, A.; Iannazzo, D.; Romeo, G. *J. Org. Chem.* **1999**, *64*, 28–36.
69. Lee, K.; Choi, Y.; Gullen, E.; Schlueter-Wirtz, S.; Schinazi, R. F.; Cheng, Y. C.; Chu, C. K. *J. Med. Chem.* **1999**, *42*, 1320–1328.
70. Lee, K.; Choi, Y.; Gumina, G.; Zhou, W.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2002**, *45*, 1313–1320.
71. Chen, X.; Zhou, W.; Schinazi, R. F.; Chu, C. K. *J. Org. Chem.* **2004**, *69*, 6034–6041.
72. Hossain, N.; Papchikhin, A.; Plavec, J.; Chattopahyaya, J. *Tetrahedron* **1993**, *49*, 10133–10156.
73. Kumamoto, H.; Tanaka, H. *J. Org. Chem.* **2002**, *67*, 3541–3547.
74. Schlawe, D.; Majdalani, A.; Velcicki, J.; Hebler, E.; Wieder, T.; Prokop, A.; Scmalz, H. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 1731–1734.
75. Ewing, D. F.; Fahmi, N.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P.; Shaw, G. *Nucleosides Nucleotides* **1999**, *18*, 2613–2630.
76. Ewing, D. F.; Fahmi, N.; Len, C.; Mackenzie, G.; Pranzo, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3561–3565.
77. Belloli, E.; Len, C.; Mackenzie, G.; Ronco, G.; Bonte, J. P.; Vaccher, C. *J. Chromatogr., A* **2001**, *943*, 91–100.
78. Ewing, D. F.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P. *Tetrahedron: Asymmetry* **2000**, *11*, 4995–5002.
79. Sélouane, A.; Vaccher, C.; Villa, P.; Postel, D.; Len, C. *Tetrahedron: Asymmetry* **2002**, *13*, 407–413.
80. Pilard, S.; Riboul, D.; Glaçon, V.; Moitessier, N.; Chapleur, Y.; Postel, D.; Len, C. *Tetrahedron: Asymmetry* **2002**, *13*, 529–537.
81. Egron, D.; Périgaud, C.; Gosselin, G.; Aubertin, A. M.; Faraj, A.; Sélouane, A.; Postel, D.; Len, C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4473–4475.

**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.

**Grahame Mackenzie** graduated with a B.Tech. and Ph.D. at the University of Bradford. His post graduate and post-doctoral research fellowship work were with Gordon Shaw at the University of Bradford and then with George Brown at the Sloan Kettering Cancer Research Institute, New York, USA. He took an appointment as Senior Lecturer at the University of Lincoln and then moved to the University of Hull, firstly as a Senior Lecturer and then as Reader in Bio-organic Chemistry. He has been a Visiting Professor at the University of Hokkaido Japan and CNRS Post Rouge, Director de Recherche at the Université de Lyon, France. Since 1992 he has been a Visiting Professor at the Université de Picardie, Jules Verne, Université d'Artois and Université de Limoges France. He has published some 130 papers in the fields of carbohydrate and nitrogen heterocyclic chemistry, particularly in relation to the synthesis of nucleosides and glycolipids. More recently his work has focused on the chemistry of plant spore materials and he is Scientific Director of Sporomex Ltd.