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Recent advances in the synthesis of fluorinated nucleosides

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Abbreviations: Ac, acetyl; AIBN, 2,2′-azobis(isobutyronitrile); AIDS, acquired immune deficiency syndrome; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BOM, benzyloxymethyl; BSA, *N*,*O*-bis(trimethylsilyl)acetamide; BSTFA, *N*,*O*-bis(trimethylsilyl)trifluoroacetamide; Bz, benzoyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; CMV, cytomegalovirus; DAST, diethylaminosulfur trifluouride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, 1,3-dicyclohexylcarbodiimide; DEAD, diethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DIBAL-H, diisobutylaluminium hydride; DIPEA, diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DMF, *N*,*N*-dimethylformamide; DMP, 2,2-dimethoxypropane; DMS, dimethyl sulfide; DMSO, dimethylsulfoxide; DMTr, dimethoxytrityl; DNA, deoxyribonucleic acid; DNP, 2,4-dinitrophenyl; DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; EBV, Epstein–Barr virus; F-TEDA-BF_4, 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]-octane bis(tetrafluoroborate); HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HMDS, hexamethyldisilazane; HMPA, hexamethylphosphoramide; HMPT, hexamethylphosphorous triamide; HSV, herpes simplex virus; HWE, Horner–Wadsworth–Emmons; LDA, lithium diisopropylamide; LiHMDS, lithium bis(trimethylsilyl)amide; LTMP, lithium tetramethylpiperidide; *m*-CPBA, *meta*-chloroperbenzoic acid; MEM, methoxyethoxymethyl; MMT (MMTr), *p*-methoxyphenyldiphenylmethyl; Ms, methanesulfonyl; NaHMDS, sodium bis(trimethylsilyl)amide; NBA, *N*-bromoacetamide; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NfF, perfluorobutanesulfonyl fluoride; NFSI, *N*-fluorobenzenesulfonimide; NMO (NMMO), *N*-methylmorpholine *N*-oxide; *N*-PSP, *N*-(phenylseleno)phthalimide; RCM, ring-closing metathesis; *p*-An, *p*-methoxyphenyl; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; Piv, pivaloyl; PMB, *p*-methoxybenzyl; *p*-TSA, *p*-toluenesulfonic acid; Py, pyridine; RNA, ribonucleic acid; SAR, structure–activity relationship; SEM, trimethylsilylethoxymethyl; TASF, tris(dimethylamino)sulfur (trimethylsilyl)difluoride; TBAF, tetrabutylammonium fluoride; TBAI, tetrabutylammonium iodide; TBDMS (TBS), *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TCDI, 1,1′-thiocarbonyldiimidazole; TEA, triethylamine; TEMPO, 2,2,6,6-tetramethylpiperidinyloxy; TEPA, triethyl phosphonoacetate; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic acid anhydride; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIPDS (TPDS), 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene); TMP, 2,2,6,6-tetramethylpiperidine; TMS, trimethylsilyl; TMSOTf, trimethylsilyl triflate; Tol, toluoyl; TPP, triphenylphosphine; Tr, triphenylmethyl (trityl); Ts, *p*-toluenesulfonyl (tosyl); VZV, varicella zoster virus.

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1. Introduction

Fluorine is one of the most abundant elements on earth. However, it occurs extremely rarely in biological compounds. Due to the specific properties of fluorine atom(s), including small steric size, high electronegativity, carbon–fluorine bond strength and sensitivity of ^{19}F NMR spectroscopy along with large ^{19}F–^{1}H coupling constants, etc., the introduction of fluorine atom(s) into many biologically active molecules can bring about remarkable and profound changes in their physical, chemical and biological properties.[1–3] For example, research has clearly demonstrated the important effects of fluorine substitution on the inter- and intramolecular forces, which affect binding of ligands, and thus introduce receptor subtype selectivity, at cholinergic and adrenergic receptors.[4–6] Fluorine substitution can also have a profound effect on drug disposition, in terms of distribution, drug clearance, route(s) and extent of drug metabolism.[7] In the past several decades, the noteworthy increase in the utilization of fluorine-containing chemicals, e.g., fluorinated materials, fluorinated amino acids, fluorinated sugars, fluorinated steroids and fluorinated nucleosides, has unambiguously illustrated the significant impact that fluorine has made on all aspects of modern life.

Known to be deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) subunits, nucleosides play key roles in neurotransmission[8] and regulation of cardiovascular activity[9] and as signalling molecules,[10] in addition to their role as intermediates for many essential cellular biosynthetic pathways. Consisting of both a base moiety and a sugar moiety, nucleosides are usually classified into two major subtypes, i.e., N-nucleosides and C-nucleosides. N-nucleosides feature a bond between the anomeric carbon of the sugar moiety and the nitrogen of the base moiety whereas C-nucleosides have a bond between the anomeric moiety and the carbon of the base moiety. Further, the nucleosides in which carbon, sulfur, phosphorus and nitrogen substitutes for the sugar ring oxygen are commonly defined as carbocyclic nucleosides,[11–15] thionucleosides,[16] phosphanucleosides[17] and azanucleosides,[18] respectively. Nucleosides and nucleoside analogues have achieved considerable success in the fight against viral infection.[19] During the last several decades, some highly biologically active nucleosides and nucleoside analogues have been synthesized, studied and used. For example, 5-iodo-2′-deoxyuridine (IDU) was licenced as the first nucleoside antiviral, and the first antiviral chemotherapeutic agent for use in humans.[20] The 2′,3′-dideoxynucleosides (ddNs) have thus far proved to be the most effective therapeutic agents against the human immunodeficiency virus (HIV)[21] and hepatitis B virus (HBV).[22,23] 3′-Azido-2′,3′-dideoxythymidine (AZT),[24] 2′,3′-dideoxyinosine (ddI)[25] and 2′,3′-dideoxycytidine (ddC)[26] have also been approved for the treatment of acquired immune deficiency syndrome (AIDS).

Fluorinated nucleosides, containing fluorine atom(s) or fluorine-containing groups in the sugar moiety or in the base moiety of nucleosides, have drawn increasing attention, due to the introduction of the fluorine atom(s) into some nucleosides resulting in a great improvement in the bioactivity and stability of the corresponding compounds. Perhaps the best known of the fluorinated nucleosides are FMAU,[27,28] FIAC,[28] FLT,[29,30] F-ddC,[31] SFDC[32] and gemcitabine (Fig. 1),[33,34] all of which have high antiherpes activities, as well as antitumour activities in some cases. Especially noteworthy is gemcitabine, which has been approved by the FDA for the treatment of inoperable pancreatic cancer and of 5-fluorouracil-resistant pancreatic cancer.[35,36] Moreover, gemcitabine in combination with cisplatin,[37] paclitaxel[38–40] and carboplatin[41,42] was indicated for the first-line treatment of patients with inoperable, locally advanced (stage IIIA or IIIB), or metastatic (stage IV) non-small cell lung cancer, patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated, and patients with advanced ovarian cancer that has relapsed at least six months after completion of platinum-based therapy, respectively. For all these reasons, fluorinated nucleosides have been the subject of intense synthetic activity. However, to the best of our knowledge, none of the formerly published reviews have systematically addressed the synthesis of fluorinated nucleosides, although many aspects of the chemistry of fluorinated nucleosides have been reviewed.[43–48] This review mainly concentrates on the synthesis of fluorinated nucleosides that

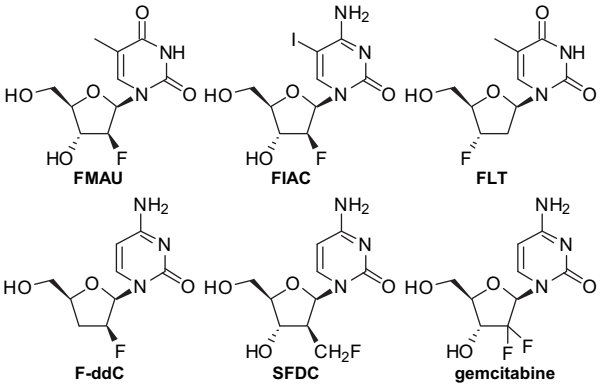


Figure 1. Highly bioactive fluorinated nucleosides.

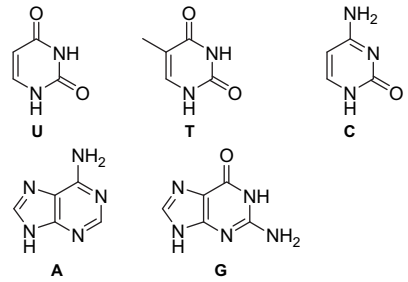


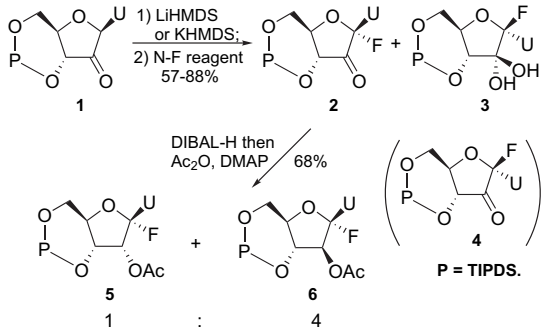
Figure 2. Structures of naturally occurring nucleic acid bases.

contain a fluorinated glycone moiety, and it does not cover a large group of nucleosides fluorinated at the nucleobase. In this review, most of the bases are the five naturally occurring nucleic acid bases, uracil (U), thymine (T), cytosine (C), adenine (A), and guanine (G) (Fig. 2).

2. Monofluorinated nucleosides

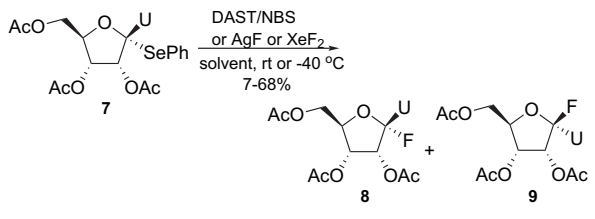
2.1. 1′-Monofluorinated nucleosides

A large number of fluoronucleoside analogues have been synthesized, and almost all of the hydrogens attached to carbons have been chemically replaced by fluorine atoms. However, the replacement of fluorine atoms at the 1′-position was seldom studied, because one might speculate that 1′-fluoronucleosides would be too unstable to be synthesized. Recently, Shuto and co-workers reported the first synthesis of 1′-fluoronucleosides (Scheme 1).[49] In their synthesis, electrophilic fluorination of the 1′-lithium enolate prepared in situ via treatment of 2′-ketouridine **1** with LiHMDS afforded an anomeric mixture of the 1′-fluoro-2′-ketouridine derivatives **2** and **4** in 57–88% yield. Compound **4** was obtained mainly as the corresponding 2′-hydrate **3** after purification by silica gel column chromatography. Reduction of the 2′-keto-moiety of **2** followed by protection of the resultant hydroxyl group gave the 1′-fluorouridine derivative **5** and its *arabino*-type congener **6** (**5**:**6**=1:4) in 68% yield.



Scheme 1.

Shuto et al. also developed another route to pyrimidine 1′-fluorouracil nucleosides.[50] This involved treatment of 2′,3′,5′-tri-*O*-acetyl-1′-phenylselenouridine **7** with DAST/NBS, AgF or XeF_2 to provide the 1′-fluorouridine triacetate **8** and its α-anomer **9** in 7–68% yield (Scheme 2). Deprotection of the synthesized 1′-fluoronucleosides under various conditions was unsuccessful, probably due to the instability of the product.

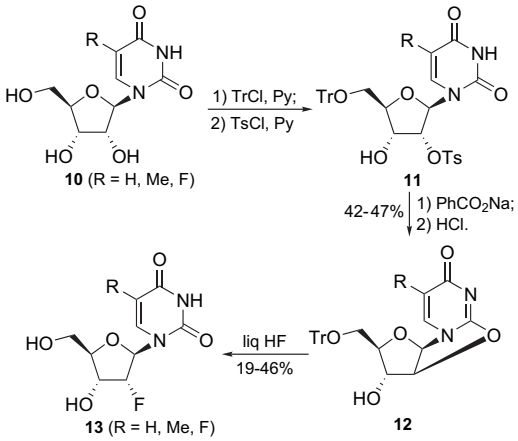


Scheme 2.

2.2. 2′-Monofluorinated nucleosides

The unique role of the substituent (hydrogen or hydroxyl) on the 2′-carbon atom in nucleoside acids as the distinguishing feature between DNA and RNA has prompted an investigation of the biological properties of nucleosides containing substituents other than hydrogen or hydroxyl at this position. Accordingly, it was interesting to study the biological properties of nucleosides containing fluorine, which could mimic both hydrogen and hydroxyl to some extent, at the 2′-position. So far, a number of 2′-monofluorinated nucleosides have been synthesized and biologically evaluated, some of which showed broad and potent biological activities. For example, FMAU and FIAC showed not only potent activities against herpes simplex virus (HSV), but also excellent activities against HBV and other viruses such as varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein–Barr virus (EBV). In addition, L-FMAU has entered phase II clinical trials for the treatment of chronic HBV infection.[27] These outstanding results motivated organic chemists and pharmaceutical workers to investigate various types of 2′-monofluorinated nucleosides bearing different functional groups.

2.2.1. 2′α-Fluoronucleosides. In 1964, Fox and co-workers first synthesized several 2′-deoxy-2′α-fluoronucleosides **13** starting from some commercially available nucleosides **10** (Scheme 3).[51] Selective protections of the hydroxyl groups in the compounds **10** in two steps gave the 2′-tosyloxy derivatives **11**, which were further subjected to treatment with $PhCO_2Na$ and HCl-mediated removal of the tosyl protecting group to deliver the 2,2′-anhydro intermediates **12** in 42–47% yield. Nucleophilic fluorination was carried out via treatment with liquid HF to afford the desired 2′α-monofluorinated nucleosides **13** in 19–46% yield.



Scheme 3.

Several years later, starting from the 2′-monofluorinated nucleoside **13** (R=H), the Fox group prepared the 2′α-fluoro-genocytidine **14** via a base-transformation procedure (Fig. 3).[52] In addition, 2′α-fluoro-2′-deoxyadenosine **15** and 2′α-fluoro-2′-deoxyguanosine **16** were also synthesized by the Ranganathan group[53] and Kawasaki's group,[54] respectively. Both groups introduced the fluorine atoms into the 2′-position via nucleophilic substitution of the corresponding triflate with TBAF.

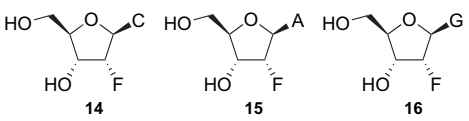
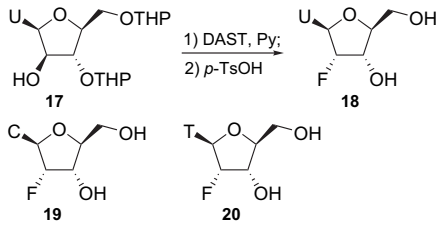


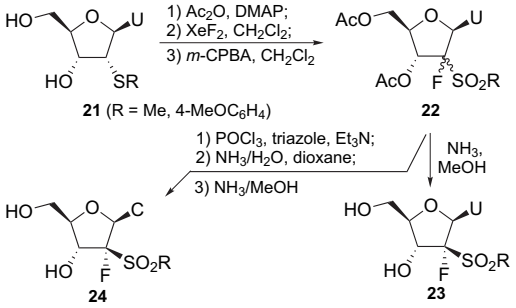
Figure 3. 2′-Monofluorinated nucleosides.

Access to L-2′-deoxy-2′α-fluororibonucleosides **18**, **19** and **20** was reported by the groups of Chu,[55] Helmling[56] and Shi,[57] respectively (Scheme 4). Their preparations utilized a similar strategy, namely, fluorination of the corresponding *arabino*-nucleosides (e.g., **17**) with DAST followed by deprotection with *p*-TsOH to afford the 2′-deoxy-2′α-fluororibonucleosides.



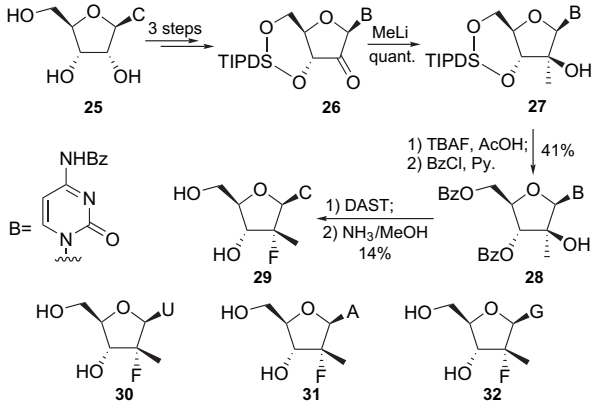
Scheme 4.

Based on the fact that dFdUrd and dFdCyd exhibited potent anticancer activity against solid tumours, Robins and co-workers accomplished the synthesis of 2′-[alkyl(or aryl)sulfonyl]-2′-deoxy-2′α-fluoronucleosides **23** and **24**, two analogues of dFdUrd and dFdCyd.[58] Starting from 2,2′-anhydro-1-β-D-*arabino*-furanosyluracil, 2′-thiouridines **21** were obtained via treatment with thiolate anions. Protection of the hydroxyl groups in the compounds **21** with acetyl groups followed by fluorination with XeF_2/CH_2Cl_2 and oxidation afforded the stable α-fluorosulfones **22**. The compounds **22** were further subjected to treatment with NH_3/MeOH or a base-transformation procedure to provide the 2′-[methyl(or 4-methoxylbenzyl)sulfonyl]-2′-deoxy-2′α-fluoronucleosides **23** and **24** (Scheme 5).



Scheme 5.

Recently, Watanabe et al. designed and synthesized β-D-2′-deoxy-2′α-fluoro-2′-*C*-methylcytidine **29** as a potential inhibitor of hepatitis C virus (HCV) replication (Scheme 6).[59] In their synthesis, the cytidine **25** was firstly converted into the 2′-ketone derivative **26** in three steps. Treatment of **26** with methyllithium gave the compound **27**. Removal of the silyl group in **27** and benzoylation of the resultant hydroxyl groups provided the compound **28**, which was subjected to fluorination with DAST and removal of the benzoyl groups with NH_3/MeOH to furnish the target nucleoside **29**. Using a similar strategy, this group also carried out the synthesis of three analogues, the uracil nucleoside **30** and the purine nucleosides **31** and **32**.[60]



Scheme 6.

A large number of 2′-deoxy-2′α-fluoronucleosides such as 2′-deoxy-2′α-fluoro-*xylo*-cytidine **33**,[61] 2′-deoxy-2′α-fluoro-5-methyl-*xylo*-uridine **34**,[62] 2′,3′-dideoxy-2′α-fluoro-3′-iodomethyl-5-methyluridine **35**,[63] 3′-azolyl-2′,3′-dideoxy-2′α-fluorouridine **36**,[64] 3′-azido-2′,3′-dideoxy-2′α-fluoro-5-methyluridine **37**, 3′-amino-2′,3′-dideoxy-2′α-fluoro-nucleosides **38**,[65,66] 3′-azidomethyl-2′,3′-dideoxy-2′α-fluoro-5-methyluridine **39** and 3′-aminomethyl-2′,3′-dideoxy-2′α-fluoro-5-methyluridine **40**[67] have been synthesized by several groups (Fig. 4). The syntheses of these nucleosides have paved the way for further investigations into the effect of 3′-substituted groups in β-D-2′-deoxy-2′α-fluoronucleosides on their bioactivities (structure–activity relationship, SAR).

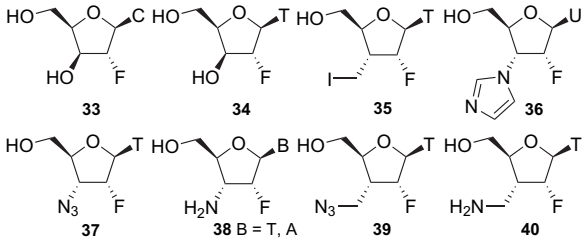
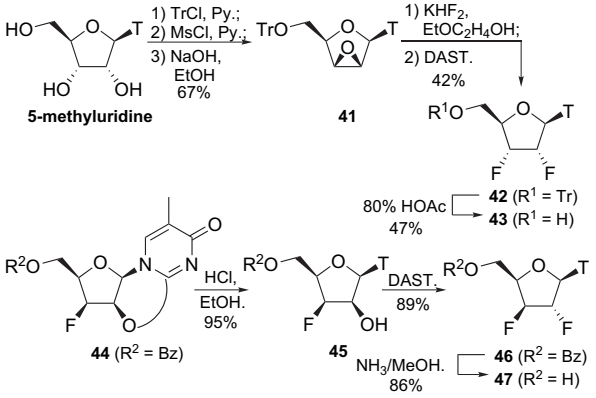


Figure 4. 2′-Deoxy-2′-fluoronucleosides.

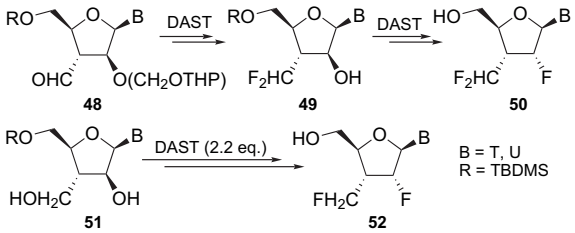
Considering that 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC) and 3′-deoxy-3′-fluorothymidine (FLT) exhibited high activities against HIV-1, Wantanabe and co-workers synthesized 2′,3′-dideoxy-2′,3′-difluoro-5-methyluridine **43** in 1991,[68] which combined the characteristics of the nucleosides F-ddC and FLT (Scheme 7). In their synthesis, the commercially available *ribo*-furanosylthymine was firstly converted into the 2′,3′-*lyxo*-epoxide **41** in three steps. Treatment of the epoxide **41** with KHF_2 in ethoxyethanol at 140 °C afforded a mixture of 2′-fluoro-*xylo* and 3′-fluoro-*arabino* nucleosides, which, without separation, was further treated with DAST to provide the protected nucleoside **42**. Removal of the trityl group with 80% HOAc at 100 °C gave the target nucleoside **43**. Two years later, Gosselin's group[69] described the synthesis of 1-(2,3-dideoxy-2,3-difluoro-β-D-*xylo*-furanosyl)thymine **47**, the diastereoisomer of nucleoside **43**. Exposure of the 2,2′-anhydro intermediate **44** to HCl/EtOH provided the lyxoside **45** in 95% yield, which was further fluorinated with DAST to give the *xylo*-difluoro nucleoside **46**. Removal of the benzoyl group in compound **46** yielded the nucleoside **47** in 86% yield.



Scheme 7.

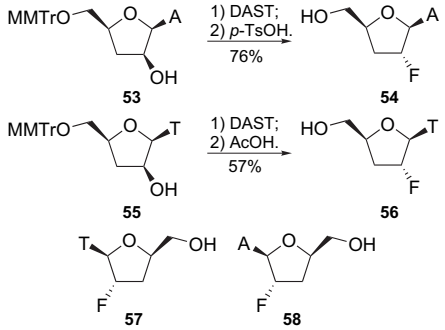
2′,3′-Dideoxy-2′α-fluoro-3′α-difluoromethyl nucleosides **50** and 2′,3′-dideoxy-2′α-fluoro-3′α-fluoromethyl nucleosides **52** were prepared from the intermediates **48** and **51**, respectively (via **49** and

52) (Scheme 8).[70] Work in Walker's laboratory featured the introduction of the difluoromethyl group and monofluoromethyl group via the fluorinations of the aldehyde group and hydroxymethyl group, respectively, with DAST.



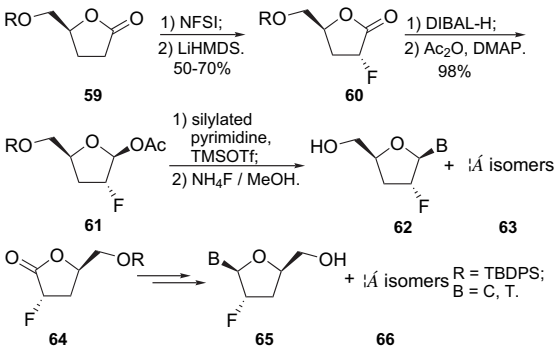
Scheme 8.

Pioneered by the De Clercq group and followed by Herdewijn et al., 2′,3′-dideoxy-2′α-fluoronucleosides **54**[71] and **56**[72] were synthesized starting from 1-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine analogue **53** and 1-(3-deoxy-β-D-*threo*-pentofuranosyl)thymine analogue **55**, respectively (Scheme 9). Both of their procedures included the introduction of a fluorine atom into the 2′α-position via fluorination with DAST and subsequent deprotection by acetic acid or *p*-toluenesulfonic acid treatment. Using a similar strategy, the L-2′,3′-dideoxy-2′α-fluoronucleosides **57**[73] and **58**[74] were also synthesized by the Gasselin group.



Scheme 9.

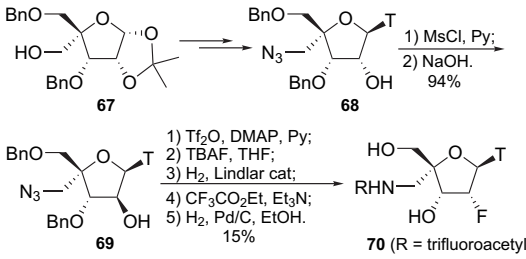
In 1998, Liotta and co-workers developed a highly diastereoselective method for the introduction of a fluorine atom into a noncarbohydrate sugar ring precursor and this methodology was successfully utilized to synthesize the 2′-fluoronucleosides (Scheme 10).[75] The electrophilic fluorination of the chiral lactone **59** with NFSI/LiHMDS diastereoselectively afforded the monofluorinated product **60** in 50–70% yield. The key intermediate **60** was reduced with DIBAL-H followed by acetylation with Ac_2O/DMAP to produce the anomeric acetate **61**. The compound **61** was used for the synthesis of 2′α-fluoro-D-nucleosides **62** and **63** by standard



Scheme 10.

Vorbrüggen methodology with TMSOTf as the Lewis acid. The L-enantiomer nucleosides **65** and **66** were also prepared, starting from the fluorinated lactone **64** using a similar synthetic route.

In order to investigate the possibility of increasing the binding affinity and nuclease resistance of oligonucleotides containing 4′*C*-substituted nucleotides towards RNA, Wengel and Pfundheller designed and synthesized the 4′-*C*-aminomethyl-2′-deoxy-2′α-fluorothymidine **70** (Scheme 11).[76] The starting material, 3,5-di-*O*-benzyl-4-*C*-hydroxymethyl-1,2-di-*O*-isopropylidene-α-D-*ribo*-furanose **67**, was firstly converted into the nucleoside **68** via the standard transformation of functional groups and Vorbrüggen methodology. Reversing of the *R* configuration of the C-2′ hydroxyl group in **68** into the *S* configuration was accomplished by mesylation of the *ribo*-configurated compound **68** followed by reaction with NaOH, and the protected *arabino*-configurated nucleoside **69** was afforded in 94% yield. The target nucleoside **70** was accessed through nucleophilic fluorination with TBAF, Lindlar reduction and subsequent removal of the protecting groups.

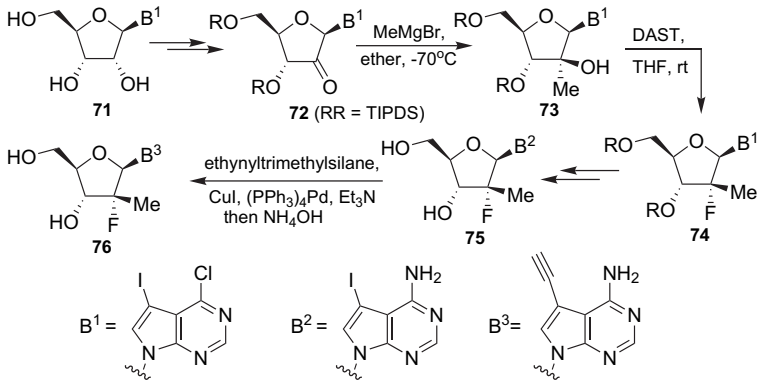


Scheme 11.

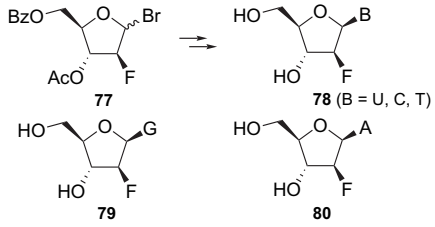
Starting from the nucleoside **71**, which was converted into ketone **72** via selective silylation and oxidation, Prhavc and coworkers accomplished the synthesis of 7-deaza-7-ethynyl-2′-deoxy-2′-fluoro-2′-*C*-methyladenosine **76** (Scheme 12).[77] The key steps of the synthesis were the selective methylation of ketone **72** with MeMgBr and subsequent fluorination of the alcohol **73** with DAST to give **74**. The final fluorinated nucleoside **76** was afforded by the coupling of the intermediate **75** with ethynyltrimethylsilane. Additionally, Prhavc and McGuigan also completed the synthesis of the corresponding nucleoside 5′-monophosphate[78] and nucleoside 5′-monophosphoramidate[79]of **76**.

2.2.2. 2′β-Fluoro nucleosides. In 1979, Fox and co-workers[28] first achieved the synthesis of 2′-deoxy-2′β-fluoro-*arabino*-furanosylpyrimidine nucleosides **78** (including the highly bioactive FMAU, B=T) (Scheme 13). Their synthetic strategy highlighted the condensation of a 2′β-fluoro bromo sugar **77** with different silylated bases. Utilizing a similar strategy to introduce the bases, the purine nucleoside analogues **79** and **80** were also prepared by the Montgomery group[80] and the Marquez group,[81] respectively, via coupling of the corresponding 2′β-fluoro bromo/chloro sugars with 2,6-dichloropurine or 6-chloropurine followed by transformation of the base moieties.

In view of the interesting fact that L-nucleosides exhibited potent biological activity and some of them showed lower toxicity profiles than their D-counterparts, a series of 2′-deoxy-2′β-fluoro-β-L-*arabino*-furanosyl pyrimidine and purine nucleosides **85** have been synthesized as potential anti-HBV agents by Chu and coworkers (Scheme 14).[82,83] This group first developed an efficient route to 1,3,5-tri-*O*-benzoyl-2-fluoro-α-L-*arabino*-furanose **84**, starting from L-xylose **81** via the intermediates **82** and **83** in 12 steps, of which the introduction of 2′β-fluorine by treatment of the compound **83** with $SOCl_2$/imidazole followed by $KHF_2/HF/H_2O$ was the key procedure. Bromination of the compound **84** followed by glycosylation and deprotection provided the target nucleosides **85**.

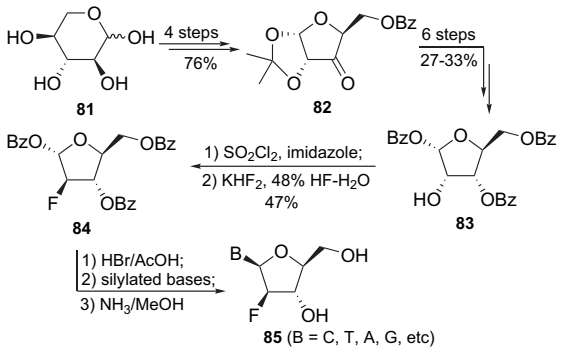


Scheme 12.



Scheme 13.

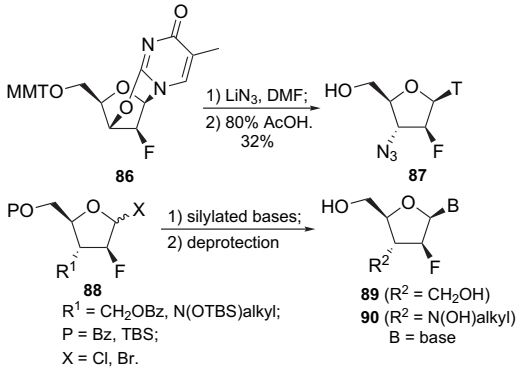
Bioactivity and structure–activity relationships (SARS, the effect of base moieties on the bioactivity) of the nucleosides **85** were also investigated.



Scheme 14.

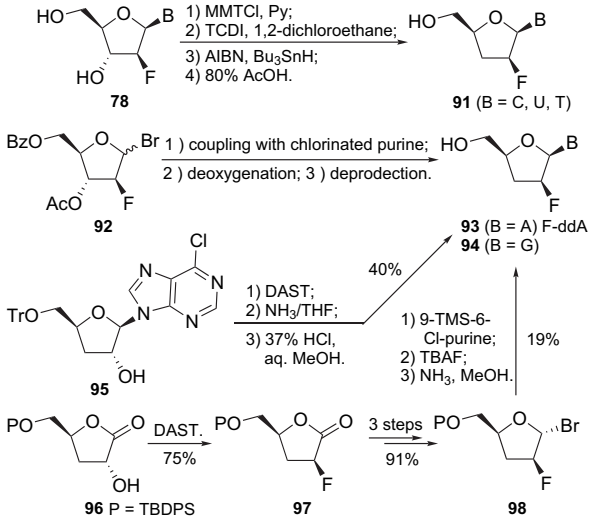
To study the effect of 3′C substitution in highly bioactive D-FMAU on the bioactivity, a large number of 3′-substituted 2′-deoxy-2′β-fluoro-*arabino*-furanosyl nucleoside analogues such as 3′-azido-2′,3′-dideoxy-2′-fluoro-5-methyl-*arabino*-uridine **87**,[84,85] 2′,3′-dideoxy-2′-fluoro-3′-*C*-hydroxymethyl-*arabino*-furanosylpyrimidine nucleosides **89**[86] and 2′,3′-dideoxy-2′-fluoro-3′-(hydroxyamino)-nucleoside analogues **90**[87,88] were synthesized by the groups of Watanabe, Sterzycki, Hassan and Zhao, respectively (Scheme 15). The nucleoside **87** was afforded by treatment of the *O*-2,3′-anhydro derivative **86** with LiN_3/DMF followed by deprotection, whereas the other nucleosides **89** and **90** were obtained via coupling of the corresponding 3′α-substituted 2′β-fluoro bromo/chloro sugars **88** with the different silylated nucleobases followed by deprotection. The bioactivities of these 3′-substituted D-FMAU analogues were also studied in detail by these groups.

In 1990, Sterzycki and co-workers synthesized the 2′,3′-dideoxy-2′β-fluoro-*arabino*-furanosylpyrimidine nucleosides **91** (including the highly bioactive F-ddC, B=C), starting from the 2′-deoxy-2′β-fluoro-*arabino*-furanosylpyrimidine nucleosides **78**.[85] Their synthesis was carried out by treatment of **78** with MMTCl, and the



Scheme 15.

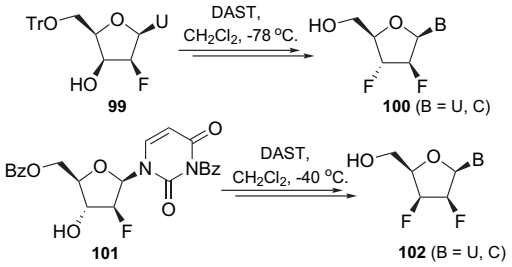
resultant protected esters were subjected to deoxygenation by reaction with 1,1′-thiocarbonyldiimidazole (TCDI), followed by reduction with Bu_3SnH and deprotection to provide the target nucleosides **91** (Scheme 16). In the same year, the purine nucleoside analogues **93** (F-ddA)[81] and **94**[89] were also prepared by the Marquez group via coupling of 3′α-acetyl-2′β-fluoro bromo sugar **92** with 2,6-dichloropurine or 6-chloropurine followed by transformation of base, deoxygenation and deprotection. It should be noted that, a decade later, Izawa's group[90,91] and Choudhury's group[92] improved the synthesis of F-ddA **93**. The process of Izawa's group featured the fluorination of the protected 6-chloro-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine **95** with DAST followed by



Scheme 16.

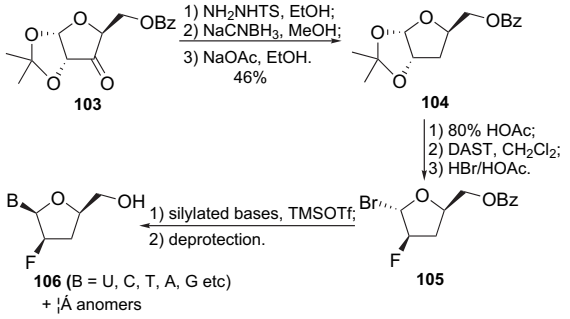
deprotection and base transformation. Choudhury's group utilized the highly *syn*-stereoselective fluorination of the lactone **96** with DAST to obtain the fluorolactone **97**, which was further converted into the bromo sugar **98** in a straightforward fashion. Introduction of the base moiety via coupling of the sugar **98** with 9-TMS-6-Cl-purine and deprotection gave F-ddA in 19% yield.

In view of the fact that FLT and F-ddA (**93**) were found to be potent nucleoside-based HIV reverse transcriptase inhibitors and both are currently at various stages of clinical development as anti-HIV agents,[93] Martin's group and Marquez et al. accomplished the syntheses of 2′,3′-dideoxy-2′, 3′-difluoro-*arabino*-furanosylpyrimidine nucleosides **100**[94] and 2′,3′-dideoxy-2′,3′-difluoro-*lyxo*-furanosylpyrimidine nucleosides **102**,[95] respectively (Scheme 17). These nucleosides combined the characteristics of FLT and F-ddA. Starting from the corresponding 2′β-fluoro-3′β-hydroxy nucleoside **99** and 2′β-fluoro-3′α-hydroxy nucleoside **101**, the target nucleosides **100** and **102**, respectively, were smoothly afforded via fluorination with DAST.



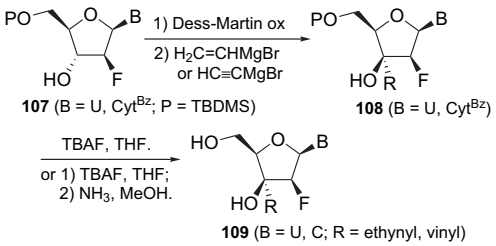
Scheme 17.

A series of 2′,3′-dideoxy-2′β-fluoro-L-*threo*-pentofuranosyl nucleosides **106** were synthesized as potential antiviral agents by the Chu group in 1999 (Scheme 18).[96] Using the Woff–Kishner methodology, the ketone **103** was first reduced to the 3-deoxy derivative **104** in 46% yield over three steps. Removal of the isopropylidene ketal of **104** followed by fluorination with DAST and bromination with HBr/HOAc afforded the key intermediate **105**. Coupling of the bromo sugar **105** with silylated bases and deprotection gave the nucleosides **106** and their α anomers.



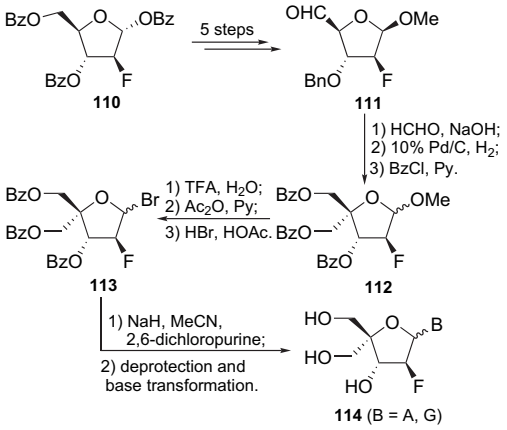
Scheme 18.

Recently, Secrist and co-workers[97] described the synthesis of several 2′-deoxy-3′-*C*-ethynyl and 3′-*C*-vinyl-2′β-fluoro-β-D-*lyxo*-furanosyl nucleosides **109** based on the knowledge that some 3′-alkyl or 3′-alkynyl branched nucleoside analogues have exhibited potent antiviral and anticancer activities. Their synthesis was accomplished via the key intermediates, the protected 2-deoxy-2′β-fluoro-β-D-*arabino*-furanosyl nucleoside analogues **107** (Scheme 19). Oxidation of the secondary alcohol **107** with Dess–Martin periodinane followed by addition, in situ, of ethynylmagnesium bromide or vinylmagnesium bromide gave the *lyxo*-adducts **108** in high stereoselectivities. Final removal of all of the protecting groups provided the target nucleosides **109**.



Scheme 19.

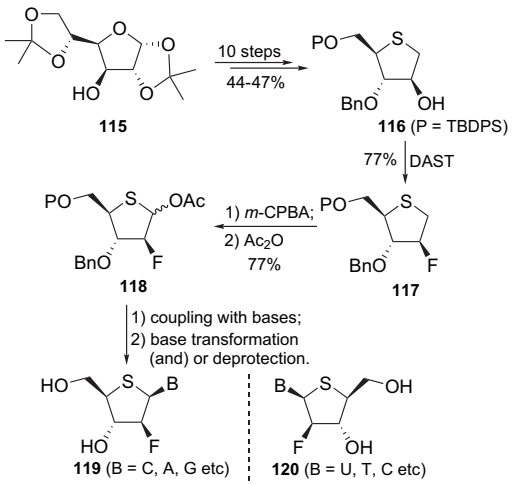
In addition to the aforementioned nucleosides **109**, Secrist's group also carried out the synthesis of several 4′-*C*-hydroxymethyl-2′β-fluoro-D-*arabino*-furanosylpurine nucleosides **114** (Scheme 20), which were further evaluated for their cytotoxicities on human tumour cell lines.[98] In their synthesis, the aldehyde **111**, which was prepared from **110** in five steps, reacted with HCHO/NaOH to afford the diol **112**. Exposure of the compound **112** to TFA/H_2O followed by acetylation and bromination of the resultant furanose delivered the bromo sugar **113**. Using the sodium salt glycosylation procedure, the nucleosides **114** were provided after deprotection and base transformation.



Scheme 20.

2.2.3. 2′-Monofluorinated thio-/carbocyclic nucleosides. Based on the well-known fact that 4′-thionucleosides are resistant to hydrolytic cleavage of glycosyl linkage catalyzed by nucleoside phosphorylase and that 3′-thiocytidine (3TC) exhibits a high bioactivity as an anti-HIV agent, Yoshimura and co-workers carried out the synthesis of many 2′-modified 2′-deoxy-4′-thionucleosides, including 2′-deoxy-2′β-fluoro-4′-thio-*arabino*-furanosyl pyrimidine and purine nucleosides **119** (Scheme 21).[99–101] Starting from the diisopropylidene-glucose **115**, the alcohol **116** was firstly accessed in 44–47% yield over 10 steps. Treatment of **116** with DAST produced the 2-deoxy-2-fluoro derivative **117** with an '*arabino*' configuration through an episulfonium intermediate. Pummerer rearrangement of the compound **117** gave the acetate **118**, which was converted into the desired nucleosides **119** after glycosylation and deprotection. In addition, the L-isomers **120** were also synthesized by Jeong's group using a similar route.[102,103]

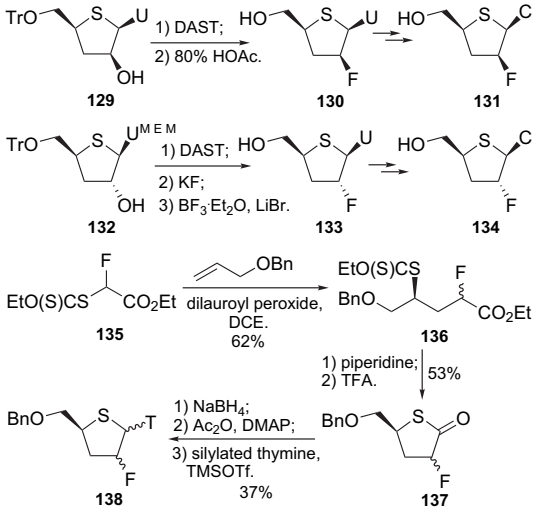
Recently, Damha's group have described an improved synthesis of 2′-deoxy-2′β-fluoro-5-methyl-4-thio-*arabino*-uridine (4′*S*-FMAU, **119**, B=T) and further pursued the conformational analysis of 4′*S*-FMAU using coupling constants and the PSEUROT program.[104] Their synthetic strategy highlighted the idea that participation of the 3′α-*O*-benzoyl protecting group in the intermediate **121** would deliver the favourable stereochemistry of the N-glycosylation reaction in nonpolar solvents, permitting a higher β/α ratio than previously observed for similar Lewis acid-catalyzed glycosylations



Scheme 21.

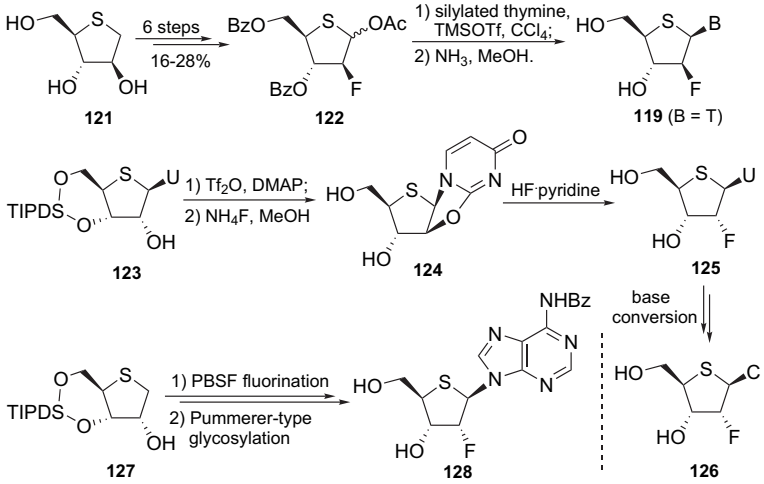
(Scheme 22). In their synthesis, 1′-*O*-acetyl derivative **122** was obtained from the 1,4-anhydro-4-thio-arabinitol **121** via a series of transformations of functional groups and Pummerer rearrangement. Just as expected, coupling of the compound **122** with silylated thymine using TMSOTf as the Lewis acid catalyst in the nonpolar solvent CCl_4 gave a comparable yield of the β product. Conformational analysis of 4′*S*-FMAU showed that the replacement of oxygen by the cognate sulfur atom at the 4′-position led to a decrease in the magnitude of the C5′-base steric effects, various *gauche* effects and a corresponding shift to a North conformation. In 2008, several 2′-deoxy-2′-fluoro-4-thio-*ribo*-nucleosides **125** and **126** were also synthesized by Minakawa et al.[105] The synthesis of **125** was accomplished via the HF·pyridine-mediated fluorination of 2,2′-*O*-anhydro-4′-thiouridine **124**, which was obtained in two steps from the 4′-thiouridine derivative **123**. Utilizing the usual method, cytosine derivative **126** was accessed from uracil derivative **125** in four steps. Additionally, this group also performed the synthesis of adenosine derivative **128** starting from compound **127** with PBSF-mediated fluorination and Pummerer-type glycosylation as the keys steps.

synthesis featured the exclusive retention of the 2′-position configuration when fluorination was pursued. The exclusive retention was attributed to a double inversion mechanism mediated by the participation of the 4-thiofuranose sulfur and a very reactive N^3-MEM anhydro intermediate. It should be mentioned that, in 2008, the Lequeux group also performed the synthesis of 2′,3′-dideoxy-2′-fluoro-4-thionucleosides from a fluoroxanthate **135**.[109] Reaction of **135** with allylic benzyl ether using dilauroyl peroxide gave the ester **136** in 62% yield. Removal of the dithiocarbonyl protecting group followed by treatment with TFA afforded the γ-thiobutyrolactone **137** in 53% yield. In a straightforward fashion, the thionucleoside analogue **138** was provided from **137** in 37% yield via reduction with $NaBH_4$, acetylation and subsequent glycosylation.



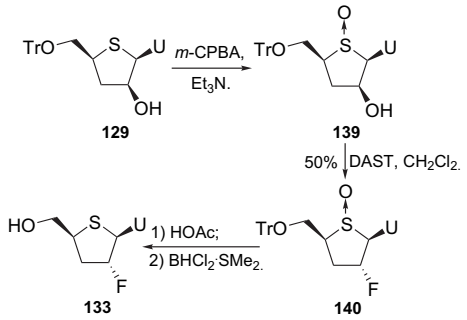
Scheme 23.

Interestingly, Marquez and Jeong also found that, after conversion of the compound **129** into the corresponding sulfoxide **139**, DAST-mediated fluorination only gave the configuration-inverted fluorinated product **140** along with the elimination product (Scheme 24).[110] This reaction further presented support for the 4-



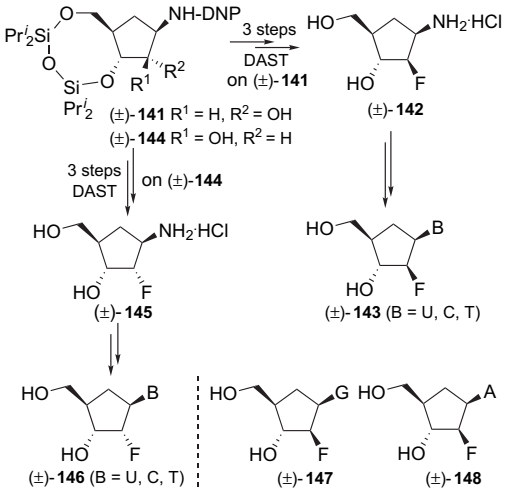
Scheme 22.

Starting from the protected 3-deoxy-4-thio-β-D-*threo*-pentofuranosyluracil **129** and the protected 3-deoxy-4-thio-β-D-*erythro*-pentofuranosyluracil **132**, 2′,3′-dideoxy-2′β-fluoro-4′-thio-β-D-nucleosides **130** and **131** and their 2′ isomers **133** and **134** were prepared, respectively, by Marquez and co-workers (Scheme 23).[106–108] Their thiofuranose sulfur involvement when the compound **129** was directly fluorinated with DAST. Furthermore, their findings provided a simple methodology to govern the stereochemical outcome of fluorination reactions according to the oxidation state of the sulfur atom.



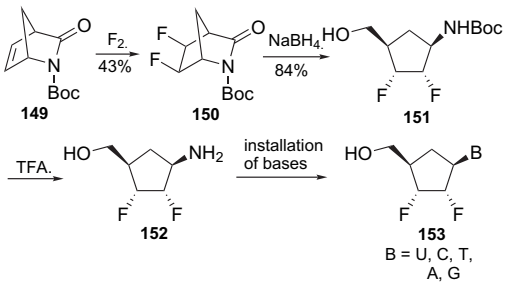
Scheme 24.

As the (±)-carbocyclic counterparts of the broad-spectrum antiviral agent FMAU, the fluorinated carbocyclic pyrimidine nucleosides (±)-**143** and (±)-**146** were synthesized by Borthwick et al., starting from the alcohols (±)-**141** and (±)-**144**, respectively (Scheme 25).[111,112] The fluorine atoms of the key aminofluorodiol hydrochlorides (±)-**142** and (±)-**145** were introduced via fluorination with DAST, and the pyrimidine bases were installed via treatment with EtOCH=C(Me)CONCO/DBU or EtOCH=CHCONCO/DBU followed by hydrochloric acid. In addition, using a similar strategy, the purine nucleoside analogue (±)-**147** was also synthesized and enzymatically resolved by the same group.[113] Later, (±)-**147**[114] and (±)-**148**[115] were also prepared by direct introduction of the 2-fluoro substituent into suitably premodified analogues using DAST as a fluorinating agent.



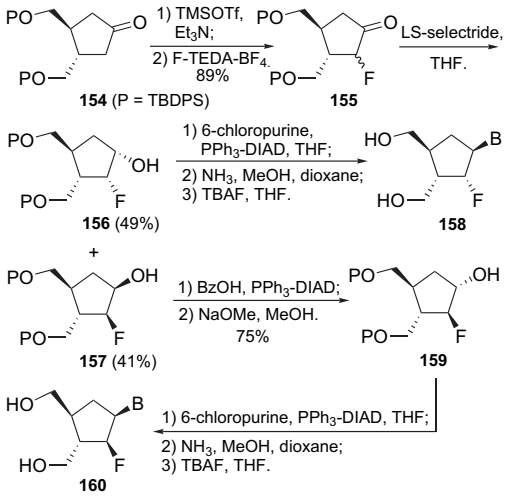
Scheme 25.

In 1994, Toyota's group found that the addition of molecular fluorine to the bicyclo[2.2.1]hept-2-ene derivative **149** afforded the corresponding *exo* adduct **150** in 43% yield, from which a series of 2′,3′-difluorinated carbocyclic nucleosides **153** were synthesized (Scheme 26).[116,117] Reductive amide-bond cleavage of **150** using $NaBH_4$ first gave the alcohol **151** in 84% yield, and this was treated with TFA to furnish the aminoalcohol **152**. Installation of pyrimidine and purine bases via standard methodology provided the target carbocyclic nucleosides **153**.



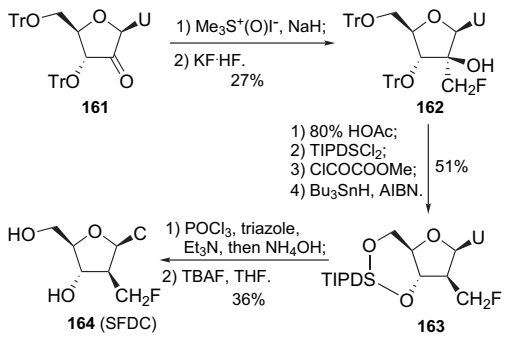
Scheme 26.

Designed as potential inhibitors of HIV and HSV, the carbocyclic 2′,3′-dideoxy-2′-fluoro-3′-*C*-hydroxymethylpurine nucleosides **158** and **160** were synthesized by Samuelsson and co-workers.[118,119] Their synthesis started from the cyclopentanone derivative **154**, which was treated with TMSOTf/Et_3N followed by F-TEDA-BF_4 to deliver the fluoroketones **155** (Scheme 27). Stereoselective reduction of the ketones **155** with LS-Selectride gave two alcohols **156** and **157**, which were separated by column chromatography. The configuration of the hydroxyl group at C-1 in **157** was inverted using a Mitsunobu reaction via treatment with benzoic acid, followed by debenzoylation to give the compound **159**. The desired purine nucleosides **158** and **160** were obtained from **156** and **159**, respectively, by means of coupling with 6-chloropurine using the Mitsunobu procedure followed by treatment with methanolic ammonia and deprotection.



Scheme 27.

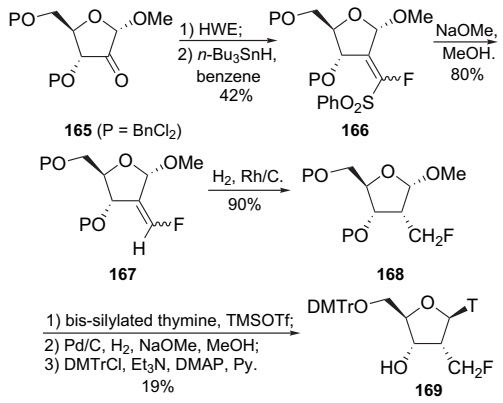
2.2.4. 2′-Monofluoromethylated nucleosides. In 1994, 2′-deoxy-2′-*C*-fluoromethylcytidine **164** (SFDC) was synthesized as a potential antineoplastic agent by Yoshimura and co-workers (Scheme 28).[32] The synthesis of the key intermediate, the fluoromethyl derivative **162**, was carried out by the reaction between the 2′-ketouridine **161** and dimethylsulfoxonium iodide followed by cleavage of the oxirane ring with KF·HF. After the protecting groups were changed, the tertiary hydroxyl group was removed by radical deoxygenation using the methyl oxalyl-Bu_3SnH system to give the 2′β-fluoromethyl



Scheme 28.

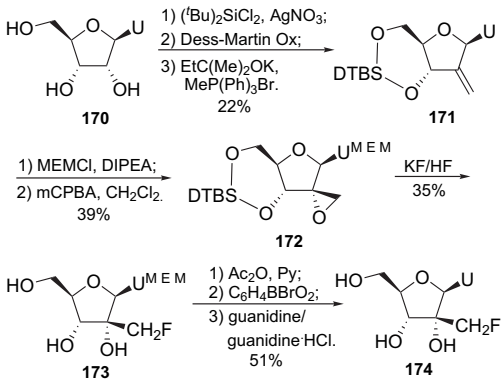
derivative **163**, which was further converted into the target nucleoside **164** via base-moiety transformation and deprotection.

In the same year, Schmit's group accomplished the synthesis of the DMTr-protected 2′-deoxy-2′α-monofluoromethyl nucleoside **169** (Scheme 29).[120] Starting from the 2′-ketone derivative **165**, the α-fluoro-α,β-unsaturated sulfone **166** was provided in two steps, of which the key step was the introduction of the terminal monofluoroolefinyl moiety via a Horner–Wadsworth–Emmons (HWE) reaction. Exposure of the compound **166** to NaOMe/MeOH afforded the fluoroolefin **167** in 80% yield. Rh/*C*-mediated catalytic hydrogenation of **167** furnished the 2′α-monofluoromethyl derivative **168** as a single stereoisomer, which was converted into the protected nucleoside **169** by coupling with bis-silylated thymine, removal of the dichlorobenzyl protecting groups and reaction with DMTrCl.



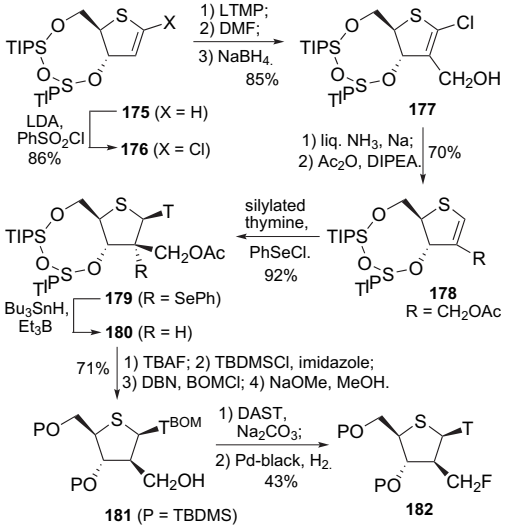
Scheme 29.

Designed as both a potentially important biological agent and a tool for biochemical analysis, 2′-*C*-β-fluoromethyluridine **174** was accessed, starting from uridine **170** by Dai and Piccirilli in 2003.[121] Their synthesis is outlined in Scheme 30 and the key steps include installation of a 2′-methylene group to give the compound **171**, protection of the uracil base with a methoxyethoxymethyl (MEM) groups, conversion into the corresponding 2′-C-α-epoxide **172** and regioselective opening of the oxirane ring with KF/HF to generate the 2′-*C*-β-fluoromethyl derivative **173**.



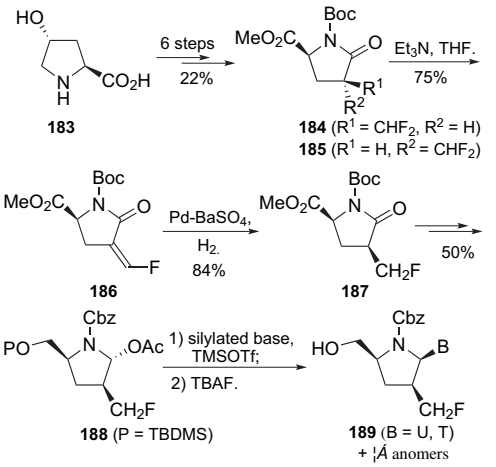
Scheme 30.

One year later, Haraguchi's group performed the synthesis of the protected 2′-*C*-β-fluoromethyl-2′-deoxy-4′-thionucleoside **182** through their pioneering methodology, which highlighted PhSeCl-mediated electrophilic glycosidation using 4-thiofuranoid glycols as glycosyl donors (Scheme 31).[122] The C-1 position of **175** was first protected via treatment with LDA/$PhSO_2Cl$ to afford the compound **176**, which was further converted into the chloroolefin **177** via treatment with LTMP followed by DMF and reduction with $NaBH_4$. Birch reduction of **177** and protection of the hydroxyl group with an acetyl group furnished the acetate **178**. Electrophilic glycosylation of **178** provided **179** with the β anomer as the main product (β/α=21:1), which was further treated with Bu_3SnH/Et_3B to afford the 4′-thiothymidine derivative **180**. After the functional groups were transformed in four steps, the resultant alcohol **181** was exposed to DAST/Na_2CO_3 to give the corresponding fluoromethyl derivative, which was hydrogenated with Pd-black as the catalyst to deliver the target compound **182**.



Scheme 31.

In 2005, 2′,3′-dideoxy-2′β-monofluoromethyl azanucleosides **189** were synthesized by Qing and Qiu (Scheme 32).[123] Their synthesis highlighted the accidentally discovered dehydrofluorination reaction caused by an organic amino base. The naturally occurring 4-hydroxyproline **183** was first converted into the difluoromethylated pyroglutamates **184** and **185** over six steps in 22% yield according to their reported methodology.[124–126] Dehydrofluorination of the mixture of esters **184** and **185** via treatment with Et_3N provided the terminal monofluoroolefin **186** in 75% yield, and this was further hydrogenated with Pd/$BaSO_4$ as catalyst to generate the *cis*-monofluoromethyl ester **187**. After the ester **187** was converted into the acetate **188** using standard procedures in six steps, coupling with silylated bases under Vorbrüggen glycosylation conditions afforded the nucleosides **189** and their α anomers.

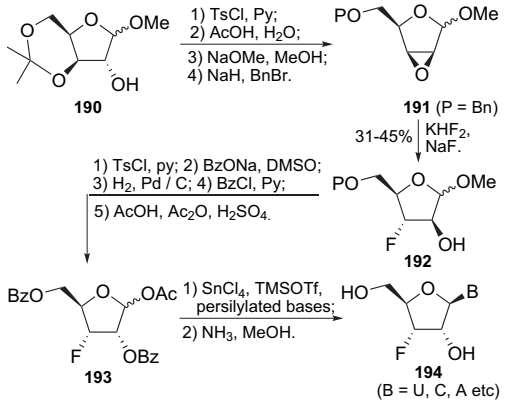


Scheme 32.

2.3. 3′-Monofluorinated nucleosides

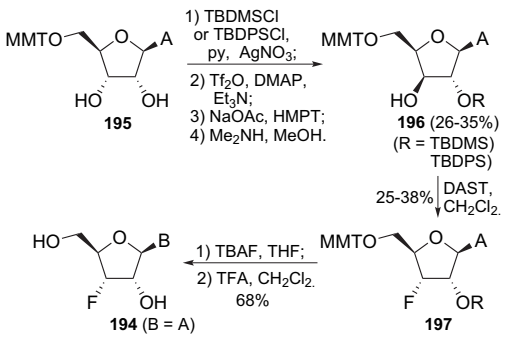
The nucleoside analogues in which the hydroxy group at C-3′ was substituted by a fluorine atom exhibited a wide range of biological properties.[127] Especially, their corresponding 5′-triphosphates acted as competitive inhibitors of some DNA polymerases by incorporating into a growing DNA chain and terminating it at a site that was strictly complementary to the corresponding template bases.[128] Some 5′-triphosphates of 3′-fluoro-modified nucleoside analogues have been shown to be very strong inhibitors of HIV and/or HBV replication at the cellular level.[129–132] However, the synthesis and investigation of the biological activity of 3′-deoxy-3′-fluoro nucleoside analogues have received relatively little attention. Since FLT was reported to be as potent as AZT against HIV in 1988,[30] the synthesis and biological activity of 3′-monofluorinated nucleosides have been greatly developed in recent years.

2.3.1. 3′α-Fluoronucleosides. De Clercq and co-workers pioneered the synthesis of 3′-deoxy-3′α-fluoro-D-*ribo*-furanosides **194** as early as 1989.[44,133,134] Starting from the methyl glycoside **190**, the epoxide **191** was provided in a straightforward fashion over four steps (Scheme 33). Treatment of the epoxide **191** with KHF_2/NaF gave the fluoride **192** in 31–45% yield, and this was converted into the acetate **193** after several operations of protecting groups involving the inversion of configuration of the C-2 position via nucleophilic substitution. The condensation between **193** and various silylated bases followed by deprotection provided the desired nucleosides **194**.



Scheme 33.

A different route to 3′-deoxy-3′α-fluoroadenosine **194** (B=A) was also described in 1990.[135] Starting from the protected adenosine **195** and through a suitably protected intermediate using triflate activation and nucleophilic displacement with NaOAc, the '*xylo*' epimers **196** were obtained in two cases after protecting the 2′-position with different silyl groups (Scheme 34). Treatment of the *xylo*



Scheme 34.

derivatives with DAST gave the corresponding 3′α-fluoro derivatives **197** with inversion of the C-3′ configuration. Desilylation by treatment of the compound **197** with TBAF and subsequent removal of the trityl group with TFA afforded the 3′-deoxy-3′α-fluoroadenosine **194**. In addition, a 3′α-fluoro-substituted guanine **194** (B=G) was also accessed by the Imbach group[136] and the Pankiewicz group,[137] who used a similar strategy, namely inversion of the C-3′ configuration of the different protected guanine derivatives followed by fluorination with DAST.

With regard to different groups (different configuration) substituted at the C-2′ position (Fig. 5), a wide range of 2′-substituted 3′-deoxy-3′α-fluoronucleosides such as 3′-deoxy-3′α-fluoro-*arabino*-adenosine **198**,[138] 2′-azolyl-2′,3′-dideoxy-3′α-fluoronucleosides **199**,[134] 2′,3′-dideoxy-3′α-fluoro-2′-*C*-methyl-5-methyluridine **200**,[139] 2′-imidazolyl-2′,3′-dideoxy-3′α-fluorouridine **201**,[64] 2′,3′-dideoxy-3′α-fluoro-2′-methylidene pyrimidine nucleosides **202**[140] and 2′-chloro-2′,3′-dideoxy-3′α-fluoronucleosides **203**[141] were also synthesized.

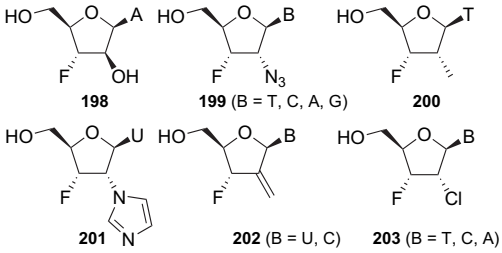
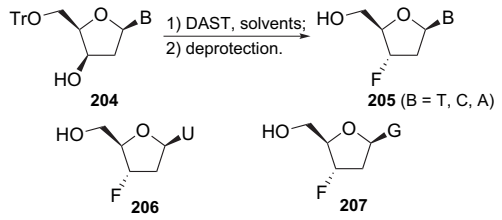


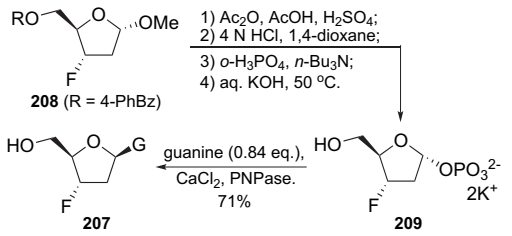
Figure 5. 2′-Substituted 3′-deoxy-3′α-fluoronucleosides with different substituent groups at the C-2′ position.

Although 3′α-fluoro-3′-deoxythymidine **205** (B=T) has been prepared via opening of the 2,3′-anhydro bond of 2,3′-anhydro-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine with HF/AlF_3 and the reaction of 3′-*O*-mesylthymidine with KHF_2 by Langen et al.,[29,142] De Clercq's group have developed a more general procedure for the synthesis of 3′α-fluoro-2′,3′-dideoxynucleosides **205**.[143] They utilized the reactions between the different 2′-deoxynucleosides **204** and DAST as the key step (Scheme 35) and, in all cases, the desired 3′α-fluoro nucleoside derivatives were obtained in moderate-to-good yields. In addition, the uridine analogue **206**[144] and the guanosine analogue **207**[145] were also prepared using a similar strategy. Notably, nucleoside **207** is now being developed as a reverse transcriptase inhibitor for HIV as well as a potential treatment for HBV.[146,147]



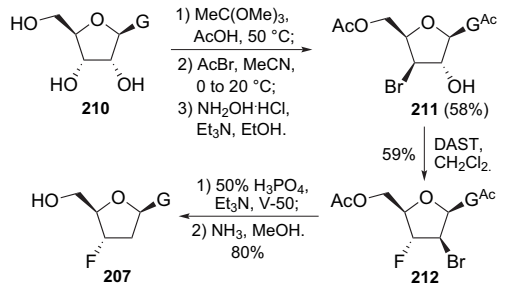
Scheme 35.

Komatsu and Araki, in 2003, described the first application of a chemo-enzymatic strategy to synthesize 2′,3′-dideoxy-3′α-fluoro-β-D-guanosine **207**.[148] 2,3-Dideoxy-3-fluoro-α-D-ribose 1-phosphate potassium salt **209** was stereoselectively prepared from the methyl furanoside **208** in four steps, of which the key step was a coupling reaction with excess *o*-H_3PO_4. In the presence of bacterial PNPase and using 0.84 equiv of guanine, the nucleoside **207** was obtained in 71% yield with the β anomer as the only product (Scheme 36).



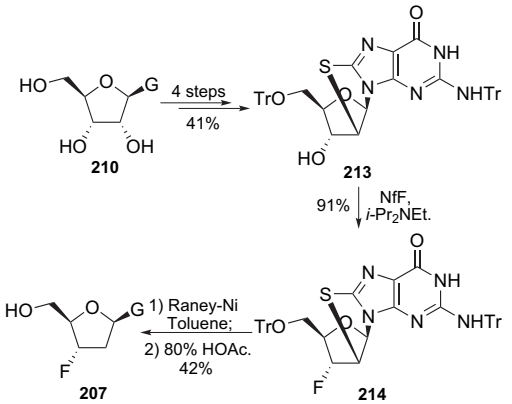
Scheme 36.

Very recently, a novel synthetic strategy for the nucleoside **207** in 27% overall yield over six steps was accomplished by Izawa's group (Scheme 37).[149] Their synthesis involved a novel rearrangement. Starting from guanosine **210**, *N*2,5′-*O*-diacetyl-3′β-bromo-3′-deoxyguanosine **211** was first obtained via acetylation, bromination and selective deacetylation. Treatment of the compound **211** with DAST gave the 3′α-fluorinated derivative **212** in 59% yield and this reaction proceeded via a shift of the bromine atom from the 3′β position to the 2′β position, with the 3′α fluorination taking place simultaneously. The debromination of **212** with 50% H_3PO_4/Et_3N followed by removal of the acetyl groups afforded the target nucleoside **207**. It should be noted that this synthetic strategy was also successfully used to synthesize 2′,3′-dideoxy-3′α-fluoro-β-D-adenosine **205** (B=A).[150,151]



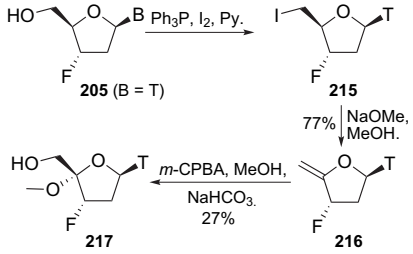
Scheme 37.

In 2006, Onishi and co-workers provided another concise route to the 3′α-fluoro-2′,3′-dideoxyguanosine **207** using 3′α-selective retentive fluorination of the 8,2′-thioanhydronucleoside **213** as the key step. This retentive fluorination proceeded through the assistance of the neighbouring group effect of the sulfur atom, i.e., by means of sulfur facilitating attack of the fluoride ion at the 3′α position rather than the 2′α position, due to the steric requirement.[152] Their method avoided the use of the explosive and expensive SF_4-related fluorinating reagent. After the 8,2′-thioanhydronucleoside **213** was prepared in four steps beginning from the guanosine **210**, treatment with an excess amount NfF in the presence of *i*-Pr_2NEt gave the desired 3′α-fluoro-3′-deoxy-8,2′-thioanhydronucleoside **214** in 91% yield (Scheme 38). Reductive desulfurization of the compound **214** was achieved by treatment with Raney Ni in toluene and, after further deprotection with 80% HOAc, the free nucleoside **207** was afforded.



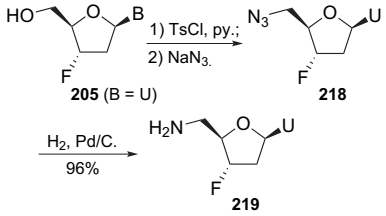
Scheme 38.

Starting from 3′α-fluoro-3′-deoxythymidine **205** (B=T), Prisbe and co-workers accessed the synthesis of a 4′-methoxy-substituted nucleoside **217** (Scheme 39).[153] In their synthesis, reaction of the nucleoside **205** (B=T) with PPh_3/I_2/pyridine produced the iodide **215**, which was further subjected to dehydroiodination via treatment with NaOMe/MeOH to afford the terminal olefin **216** in 77% yield. Final epoxidation of the compound **216** with *m*-CPBA followed by in situ opening of the resultant epoxide provided the nucleoside **217** in 27% yield.



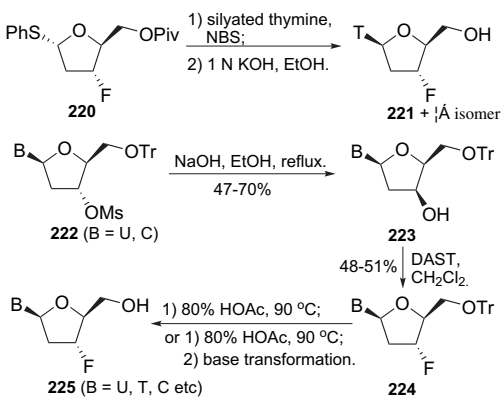
Scheme 39.

When the hydroxyl group in the 5′ position in 3′-fluoro-3′-deoxyuridine **205** (B=U) was replaced by an amine group, the resultant nucleoside **219** was synthesized and further utilized to prepare the analogues of deoxyuridine monophosphate (dUMP), which has been shown to be an inhibitor of trypanosomal enzymes.[154] Tosylation of **205** (B=U) followed by treatment with sodium azide generated the azide **218**, which underwent catalytic hydrogenation to afford the desired nucleoside **219** (Scheme 40).



Scheme 40.

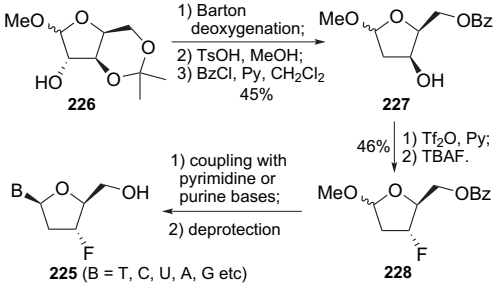
In view of the high bioactivities of 2′,3′-dideoxy-3′α-fluoro-β-D-nucleosides **205**, their L-counterparts, 2′,3′-dideoxy-3′α-fluoro-β-L-nucleosides **221**[139] and **225**,[155] were also synthesized from the compounds **220** and **222** by the Sugimura group and the Matthes group, respectively (Scheme 41). The synthesis of the Sugimura



Scheme 41.

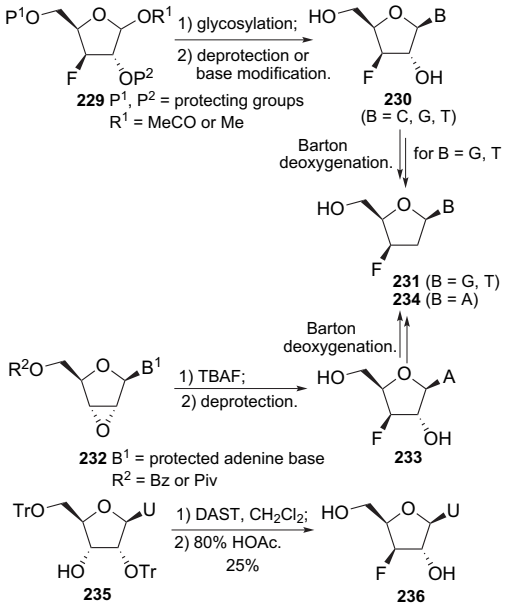
group was realized by a coupling reaction of the phenyl 3-fluoro-1-thiopentofuranoside **220** with silylated thymine by activation with NBS, and this coupling reaction preferentially resulted in the β isomer. Starting from the protected 2′-deoxy-β-L-nucleosides **222**, Matthes et al. first inverted the configuration in the 3′-position by the action of NaOH/EtOH to provide the 1-(2-deoxy-5-*O*-trityl-β-L-*threo*-pentofuranosyl)nucleosides **223**, which were further fluorinated with DAST to generate the desired fluoro compounds **224**. Detritylation and/or base transformation finally gave the 2′,3′-dideoxy-3′α-fluoro-β-L-nucleosides **225**.

In 2000, Chu's group developed another synthetic route to a series of 2′,3′-dideoxy-3′α-fluoro-β-L-nucleosides **225** starting from the key intermediate **226**,[156] which was prepared by their methodology utilizing the inexpensive D-sorbitol as starting material in four steps. Compound **226** was converted into the alcohol **227** in 45% yield through a Barton-type deoxygenation followed by acidic hydrolysis and selective protection of the hydroxyl group (Scheme 42). Fluorination of the compound **227** was accomplished with TBAF via the corresponding triflate to afford the key intermediate **228**, which was condensed with pyrimidine or purine bases, then deprotected to give the desired nucleosides **225**.



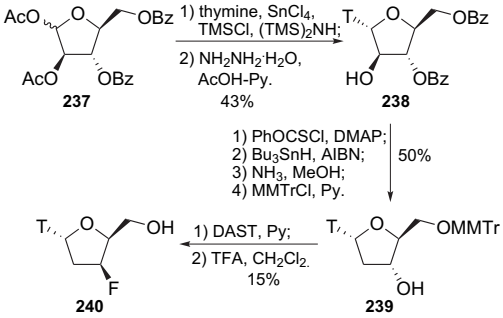
Scheme 42.

2.3.2. 3′β-Fluoro nucleosides. Usually, most of the methodologies which were used to synthesize the 3′α-fluoronucleosides could also be successfully utilized for the preparation of the 3′β-fluoro nucleosides. 3′-Deoxy-3′β-fluoro-β-D-*xylo*-furanosides bearing natural heterocyclic bases were synthesized in two traditional ways. Nucleosides, such as **230**,[61,69,157] were prepared through glycosylation of the corresponding fluorinated furanoses **229**, while the nucleosides **233**[158] and **236**[159] were obtained by means of fluorination of pre-modified nucleoside analogues **232** and **235** (Scheme 43). In addition, starting from the 3′-deoxy-3′β-fluoro-β-D-*xylo*-furanosides **230** and **233**, 2′,3′-dideoxy-3′β-fluoro-β-D-*xylo*-furanosides **231** and **234** were also afforded through a Barton-type reductive deoxygenation.[69,72]



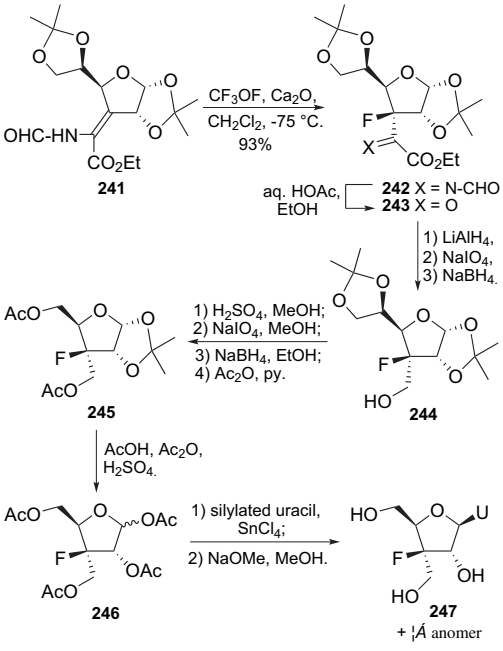
Scheme 43.

In 1991, Imbach and co-workers synthesized 2′,3′-dideoxy-3′β-fluoro-α-L-thymidine **240** (Scheme 44).[160] Utilizing their own methodology, 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-*arabino*-furanose **237** was first prepared. Condensation of **237** with thymine yielded the α-nucleoside anomer as the main product, which was selectively 2′-*O*-deacylated with hydrazine hydrate in a buffered acetic acid–pyridine mixture to generate the compound **238**. Deoxygenation of **238** followed by removal of the benzoyl group using NH_3/MeOH and selective protection of the 5′-hydroxyl group with a trityl group provided the intermediate **239** in 50% yield. Fluorination of the compound **239** with DAST in CH_2Cl_2 and deprotection gave the target 3′β-fluoro-α-L-thymidine **240**.



Scheme 44.

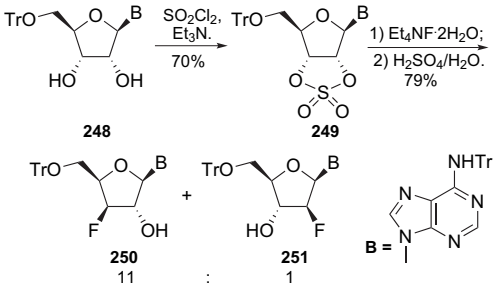
Starting from the pre-modified α-D-glucofuranose **241**, Brink's group completed the synthesis of 3′-deoxy-3′β-fluoro-3′-*C*-hydroxymethyl-β-D-uridine **247**.[161,162] Their method highlighted the stereospecific introduction of fluorine at the branching point of a branched-chain sugar (Scheme 45). Exposure of the pre-modified compound **241** to trifluoro(fluoroxy)methane using dry and ethanol-free CH_2Cl_2 as the solvent yielded the fluorinated *N*-formylimine **242** in high yield, which was converted into the more stable oxo-ester



Scheme 45.

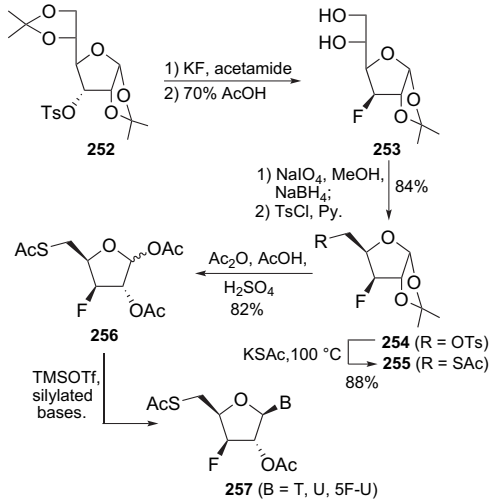
243 by mild hydrolysis. Reaction of **243** with $LiAlH_4$ followed by glycol cleavage with $NaIO_4$ and further reduction of the resultant aldehyde group with $NaBH_4$ provided the primary alcohol **244**. Subjecting **244** to selective removal of the isopropylidene ketal and further usual transformation of the functional groups furnished the acetate **245**. Hydrolysis of the compound **245** and simultaneous protection of the in situ-generated hydroxyl groups afforded the anomeric mixture **246**. Glycosylation of the mixture **246** using the modified Hilbert–Johnson procedure followed by removal of the acetyl groups provided the desired nucleoside **247** and its α isomer.

In 2002, Fuentes and co-workers found that nucleophilic opening of nucleoside-derived cyclic sulfates was a regio- and stereoselective method for preparing 3′β-fluoro nucleoside derivatives.[163] The nucleoside derivative **248**, prepared by tritylation of adenosine, was treated with SO_2Cl_2/Et_3N to provide the cyclic sulfate **249** as the sole product. The opening reaction of the compound **249** by reaction with tetraethylammonium fluoride dihydrate in acetone gave two regioisomers **250** and **251** in a ratio of 11:1 (Scheme 46). This good regioselectivity was mainly attributed to the larger steric hindrance at position C-2′ rather than at C-3′.



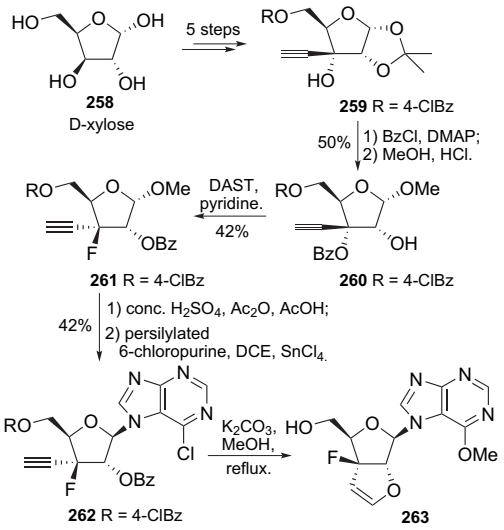
Scheme 46.

Very recently, an efficient synthesis of 3-fluoro-5-thio-*xylo*-furanosyl nucleosides **257** was described by Komiotis and coworkers.[164] In their synthesis, the 3′β-fluorine atom was introduced via treatment of the tosylate **252** with KF/acetamide (Scheme 47). The resultant fluoride **253** was subjected to periodate oxidation, borohydride reduction and sulfonylation to afford the intermediate **254** in 84% yield. After thioacetation of the compound **254** (to form **255**) and acetolysis, the yielded acetate **256** was condensed with silylated pyrimidine bases to give the target nucleosides **257**. Biological assays demonstrated that the nucleosides **257** were good candidates for the development of potential antiviral agents, as significantly lower concentrations of these agents were required with respect to AZT.



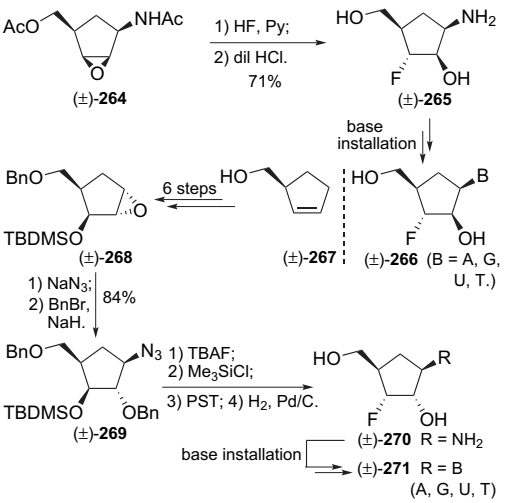
Scheme 47.

Very recently, Chang et al. accomplished the synthesis of a 3′-deoxy-3′-fluoro-2′-*O*,3′-*C*-vinylene-linked bicycle purine nucleoside (Scheme 48).[165] Their synthesis commenced with D-xylose **258**, which was converted to the 3β-*C*-ethynyl sugar **259** in five steps according to the reported procedure. Benzoylation of **259** and subsequent methanolysis with concentrated HCl gave the intermediate **260**. A neighbouring-group-participating fluorination of **260** mediated by DAST provided the 3-fluoro-3-deoxy-3α-*C*-ethynyl sugar **261** in 42% yield. Acetolysis of **261** followed by condensation with persilylated 6-chloropurine furnished the purine derivative **262**. Treatment of compound **262** with K_2CO_3 in MeOH at 65 °C finalized the synthesis of the fluorinated bicyclic nucleoside **263** in 55% yield. Chang et al. proposed that the formation of the bicyclic ring involved an intramolecular cycloaddition induced by fluorine.



Scheme 48.

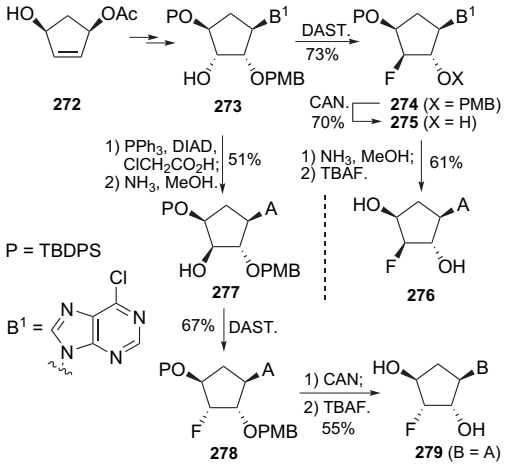
2.3.3. 3′-Monofluorinated thio-/carbocyclic nucleosides. A series of carbocyclic analogues of nucleosides substituted at the 3′-position with a fluorine atom have been synthesized by the Morizwa group (Scheme 49).[166] Their synthetic strategy featured the preparation of two key intermediates (±)-**265** and (±)-**269** by means of the regio- and stereoselective ring opening of epoxides (±)-**264** and (±)-**268** with HF/pyridine and NaN_3, respectively. Epoxide (±)-**268** was prepared from compound (±)-**267** in six steps. Conversion of the TBDMS group in (±)-**269** into a TMS group and further fluorination



Scheme 49.

with piperidinosulfur trifluouride (PST) gave the fluorinated azide, which was hydrogenated with Pd/C as catalyst to yield the fluoro amino diol (±)-**270**. Finally, the racemic carbocyclic analogues (±)-**266** of 3′-deoxy-3′α-fluoro-*ribo*-furanosides and the carbocyclic analogues (±)-**271** of 3′-deoxy-3′α-fluoro-*arabino*-furanosides were provided via installation of the different bases from the amine groups of the fluoro amino diols (±)-**265** and (±)-**270** using the general reaction procedures.

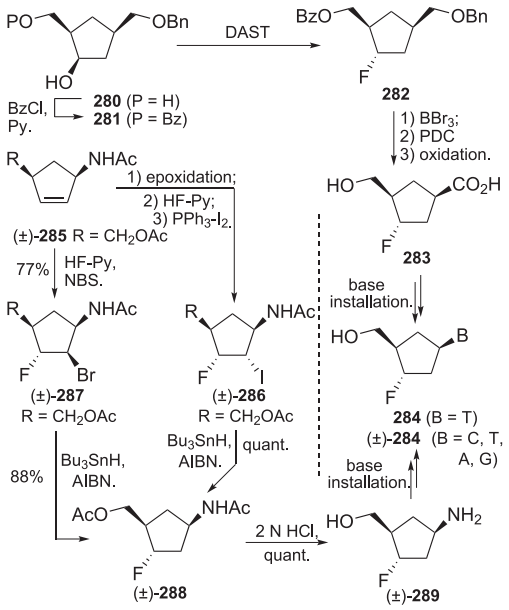
Very recently, Schneller et al. accomplished the synthesis of the carbocyclic 3′-deoxy-3′β-fluoroadenosine **276** and the carbocyclic 3′-deoxy-3′α-fluoroadenosine **279** (B=A).[167] The key synthetic steps included the preparation of the alcohol **273** from (+)-(1*R*, 4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate **272** via the introduction of 6-chloropurine base using a coupling reaction and the subsequent dihydroxylation with OsO_4/NMO (Scheme 50). Fluorination of the compound **273** with DAST yielded the fluorinated derivative **274**, which was treated with CAN to give the compound **275**. The alcohol **275** was subjected to ammonolysis and subsequent TBAF-promoted desilylation to generate the desired carbocyclic 3′-deoxy-3′β-fluoroadenosine **276**. In addition, after inversion of the C-4′ hydroxyl group in the compound **273** via a Mitsunobu reaction, the isomeric carbocyclic nucleoside **279** (B=A) was also prepared by means of a similar route via intermediates **277** and **278**.



Scheme 50.

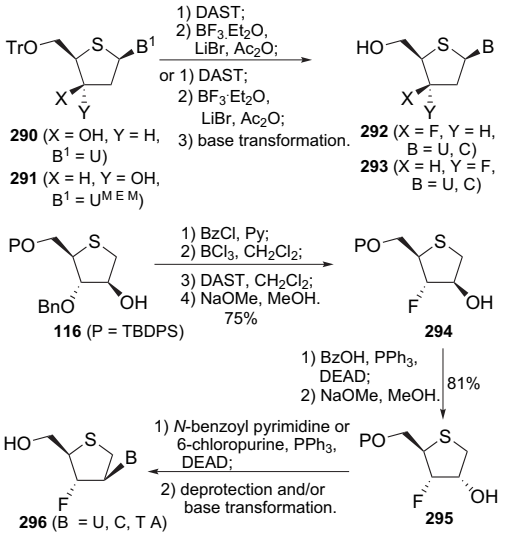
Although the carbocyclic 2′,3′-deoxy-3′α-fluorothymidine **284** (B=T) was successfully accessed by the Griengl group in 1988 via DAST-mediated fluorination of compound **281** and installation of a thymine base from the carboxyl group (amino group) of compound **283** as the key steps (Scheme 51),[168] Morizawa et al. presented another route to the racemic carbocyclic nucleoside (±)-**284** (B=T) and other base analogues, starting from *cis*-4β-acetamidocyclopent-2-enemethyl acetate (±)-**285**.[169] They prepared the key aminoalcohol (±)-**289** through two different strategies, one of which was the regioselective ring opening of epoxide with HF-Py followed by dehydroxylation via the iodide (±)-**286**; the other strategy involved the regioselective bromofluorination using HF-Py/NBS followed by reductive debromination of the resultant compound (±)-**287** to yield the fluorinated compound (±)-**288**. The target carbocyclic nucleosides (±)-**284** were finally provided through installation of different bases from the amino group of (±)-**289** using standard procedures.

After Marquez et al. completed the synthesis of 2′,3′-dideoxy-3′-fluoro-4-thionucleosides **292** and **293** via fluorination of the protected 2′-deoxy-4-thionucleosides **290** and **291** with DAST in 1994,[106,107] very recently, Jeong's group designed and synthesized the novel *iso*-D-2′,3′-dideoxy-3′α-fluorothianucleoside derivatives **296** (Scheme 52).[170] Starting from 1,4-anhydro-4-thioarabitol



Scheme 51.

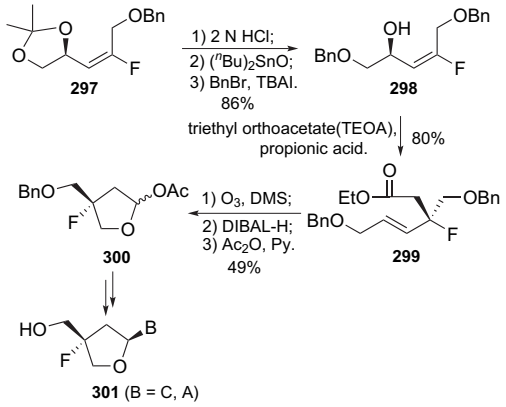
116(see Scheme 21), 4-fluoro-tetrahydro-thiophen-3-ol **294** was first synthesized in four steps, which included DAST-mediated fluorination with the desired 'α' stereochemistry as product through a double-inversion mechanism by the nucleophilic participation of the ring sulfur atom. The alcohol **294** was used for coupling with $PhCO_2H$ under Mitsunobu conditions and the configuration-inverted product **295** was afforded after removal of the Bz group. A Mitsunobu reaction was further used for the installation of pyrimidine and purine bases into the C-2′ position, and the desired β-nucleosides **296** were provided after base transformation and removal of the protecting groups.



Scheme 52.

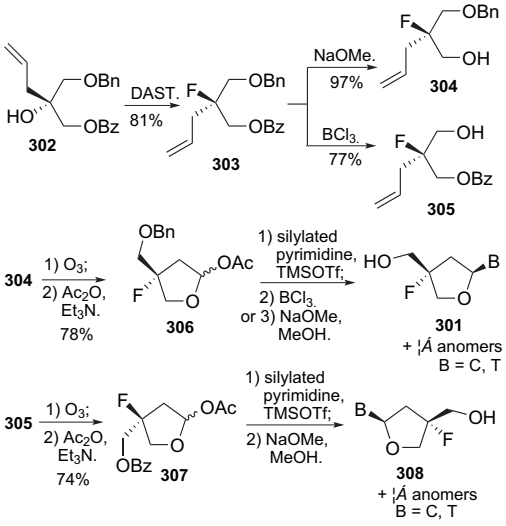
In 1998, Chu and co-workers accomplished the enantiomeric synthesis of 3′-fluoro-apionucleosides **301** (B=C, A) using a Claisen rearrangement[171] (apionucleosides, also named isonucleosides, are regioisomers of natural nucleosides by transposition of the hydroxylmethyl group from the normal 4′-position to the 3′-position; in this review, this type of nucleoside has been classified into carbocyclic nucleosides). After the (*E*)-α,β-unsaturated fluoroethyl ester **297** was converted into the allylic alcohol **298** (Scheme 53), a Claisen rearrangement reaction by treatment of the compound

298 with excess TEOA and a catalytic amount of propionic acid delivered the key intermediate, γ,δ-unsaturated *tert*-fluoroethyl ester **299**, in 90% ee, which was further subjected to ozonolysis, DIBAL-H reduction and subsequent acetylation to afford the acetate **300**. Glycosylation of the intermediate **300** with silylated N^4-benzoylcytosine or 6-chloropurine followed by deprotection gave the desired 3′-fluoro-apionucleosides **301**.



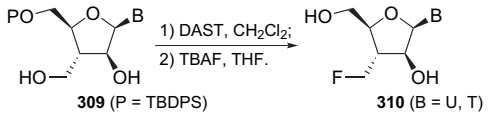
Scheme 53.

Interestingly, Jeong's group have recently developed another route to enantiomercially pure 3′-fluoro-apionucleosides **301** and **308**[172] after the racemic (±)-3′-fluoro-apionucleosides[173] were prepared in 1998. The key points of Jeong's novel strategy were the enantiospecific fluorination of the *tert*-alcohol **302** with DAST and the orthogonal protection/deprotection of the versatile diol **303** (Scheme 54). The enantiospecific fluorination of the *tert*-alcohol **302** produced **303** in 81% yield, which underwent selective deprotection to afford the primary alcohols **304** and **305**. Ozonolysis of the double bonds in **304** and **305**, and subsequent acetylation with Ac_2O gave the fluoroapiofuranosyl acetates **306** and **307**, respectively. The syntheses of the target nucleosides **301** (B=C, T) and **308** were finalized after glycosylation of **306** and **307** followed by deprotection, respectively.

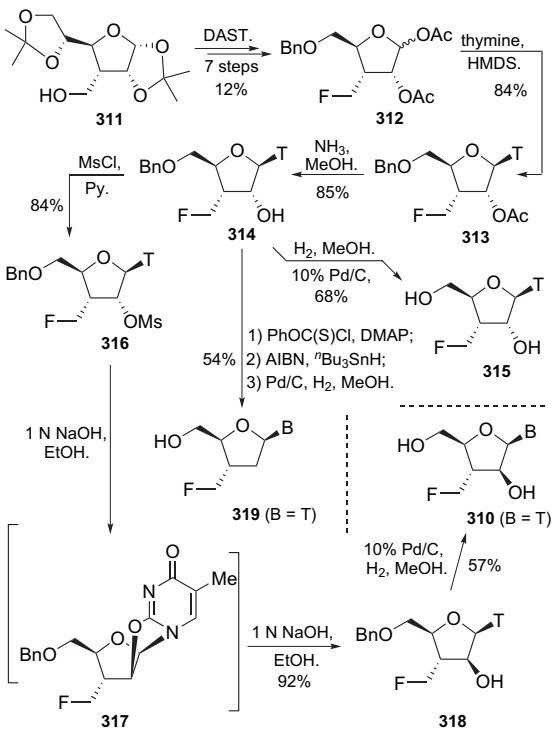


Scheme 54.

2.3.4. 3′-Monofluoromethylated nucleosides. After Walker's group completed the synthesis of 3′-deoxy-3′-*C*-fluoromethylnucleosides **310** (B=U, T), through fluorination of 3′-deoxy-3′-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl nucleoside derivatives **309** followed by deprotection, in 1990 (Scheme 55),[70] Lin and co-workers developed another route to 3′-deoxy-3′-*C*-fluoromethylnucleosides.[174] Lin's work commenced with the 3-deoxy-3-hydroxymethyl derivative **311**, which was subjected to fluorination with DAST and subsequent straightforward transformation of the functional groups to furnish the key intermediate 3-deoxy-3-fluoromethyl sugar derivative **312** (Scheme 56). Glycosylation of the compound **312** with thymine using the methodology of Vorbrüggen and Bennua gave the protected nucleoside **313**, which was further deblocked by treatment with NH_3/MeOH followed by hydrogenation to provide the 3′-deoxy-3′-*C*-fluoromethylnucleoside **315**. In addition, once the mesylate **316**, obtained through mesylation of the alcohol **314**, was treated with NaOH/EtOH (reflux), inversion of the 2′-hydroxyl configuration was accomplished to yield the product **318** via the 2,2′-anhydro intermediate **317**. Hydrogenation of **318** produced the epimer **310** (B=T) of the nucleoside **315**. Furthermore, a Barton-type deoxygenation of the compound **314** offered an entry to the 2′,3′-dideoxy-3′-*C*-fluoromethylnucleoside **319**.



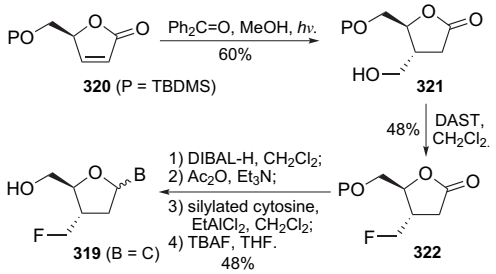
Scheme 55.



Scheme 56.

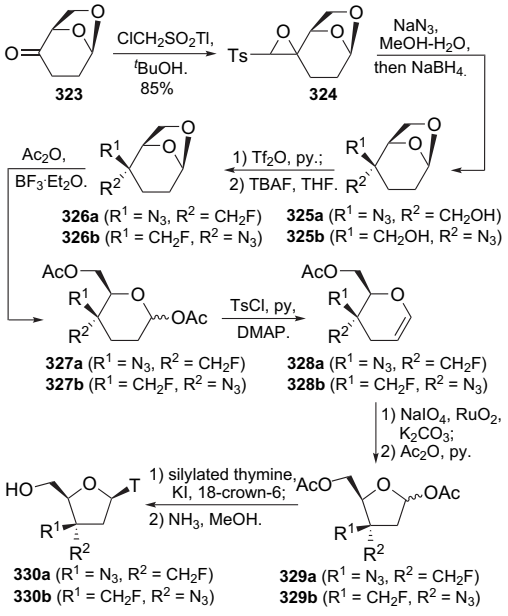
It should be noted that, although access to 2′,3′-dideoxy-3′-*C*-fluoromethylnucleoside **319** (B=T) was also developed by the Van Calenbergh group[175] using a similar synthetic route to that of the Lin group, Mann and co-workers have presented another synthetic route to 2′,3′-dideoxy-3′-*C*-fluoromethylnucleoside **319** (B=C). Mann's strategy highlighted a regiospecific and highly stereocontrolled photocatalysed addition reaction (Scheme 57).[176] Starting from the 5-substituted 2,5-dihydrofuran-2-one **320**, the key intermediate **321** was provided in 60% yield with high regio- and stereoselectivity on treatment with Ph_2C=O/MeOH under irradiation. Fluorination of the lactone **321** with DAST produced the

fluoromethyl compound **322** in 48% yield, which was further converted into the 2′,3′-dideoxy-3′-*C*-fluoromethylnucleoside **319** (B=C) in four steps using a general methodology.



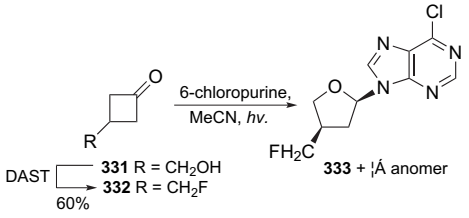
Scheme 57.

In 1999, an efficient synthetic route to the 2′,3′-dideoxy-3′-fluoromethyl-3′-azidothymines **330a–b** was discovered by Ton-That,[177] whose strategy involved the regioselective ring opening of the tosyl-epoxide derivative **324**, obtained through treatment of the ulose **323** with $ClCH_2SO_2Tl/^tBuOH$ (Scheme 58). Reaction of the α,β-epoxy-sulphone **324** with NaN_3 and subsequent reduction of the resultant α-azido-aldehyde intermediates gave the α-azido-hydroxymethyl derivatives **325a-b**, which were converted into the α-azido-fluoromethyl derivatives **326a** and **326b**, respectively, by exposure of their corresponding triflates to TBAF. Acetolysis of **326a** and **326b** with $Ac_2O/BF_3\cdot Et_2O$ generated the branched-chain acetylated sugars **327a** and **327b**, respectively. Treatment of **327a** and **327b** with TsCl/Py/DMAP afforded the internal enol ethers **328a** and **328b**, respectively, which were subjected to oxidative cleavage by a catalytic $RuO_2/NaIO_4$ method and further acetylation of the resultant lactols to yield the 2,3-dideoxyfuranosyl derivatives **329a** and **329b**, respectively. Condensation of the compounds **329a** and **329b** with silylated thymine followed by deprotection and separation of the anomers gave the target nucleosides **330a–b**.



Scheme 58.

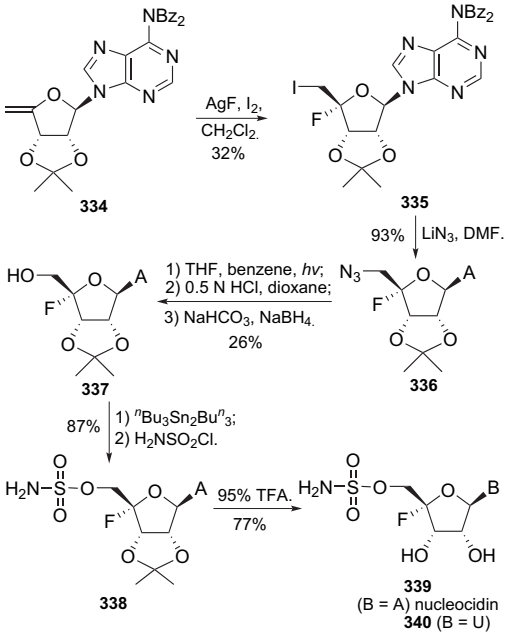
Recently, Lee-Ruff and Ghazi have reported the synthesis of a 2′,3′-dideoxy-3′-fluoromethyl-D-*erythro*-furanoside **333** through a photochemical ring-opening reaction.[178] Their synthesis commenced with the hydroxymethylcyclobutanone **331**, which was fluorinated with DAST to yield the 3-fluoromethylcyclobutanone **332** in 60% yield (Scheme 59). The fluoromethylated derivative **332** was subjected to UV irradiation in the presence of 6-chloropurine to afford the fluoronucleoside analogue **333** and its α anomer.



Scheme 59.

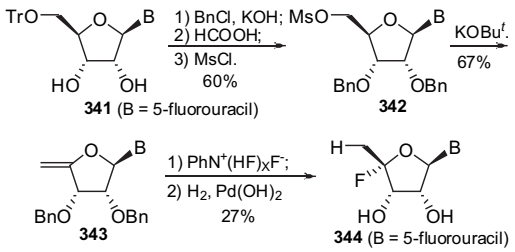
2.4. 4′-Monofluorinated and 4′-fluoromethylated nucleosides

Although the antitrypanosomal antibiotic and potent inhibitor of protein biosynthesis,[179] nucleocidin **339**, was isolated from *Streptomyces calvus* in 1957, its structure was confirmed by Morton about 10 years later.[180] So far, nucleocidin is the only fluorinated nucleoside analogue isolated from a natural organism. In 1976, Moffatt and co-workers first accomplished its synthesis, starting from the protected β-D-*erythro*-pent-4-enofuranosyladenine derivative **334** in eight steps (Scheme 60).[181] In their synthesis, reaction of the compound **334** with IF, generated in situ from AgF/I_2, gave the 4′-fluoro-5′-deoxy-5′-iodo nucleoside **335** in 32% yield, which was further subjected to treatment with LiN_3/DMF to furnish the 4′-fluoro-5′-azido-nucleoside analogue **336** in high yield. Conversion of the compound **336** into the 4′-fluoro-2′, 3′-*O*-isopropylideneadenosine **337** was fulfilled via photolysis followed by acidic hydrolysis and borohydride reduction. Exposure of the compound **337** to $Bu_3SnSnBu_3$ and subsequent treatment with an excess of sulfamoyl chloride afforded the 4′-fluoro-5′-*O*-sulfamoyladeosine derivative **338**, which was deprotected with 95% TFA to provide nucleocidin **339** as a monohydrate in 77% yield. In addition, the uracil analogue **340** and its corresponding phosphate ester analogue were also prepared by Moffatt's group using a similar route.[182] It should be noted that, in 1993, Maguire and co-workers modified the procedure of the Moffatt group to synthesize nucleocidin **339** and other nucleocidin analogues.[183]



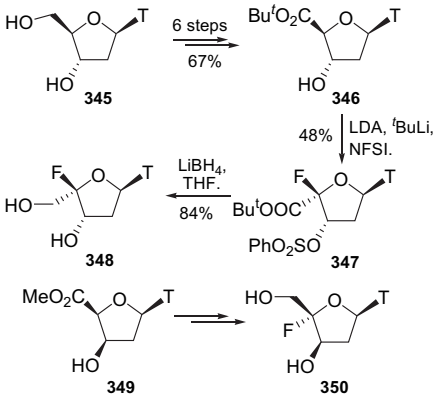
Scheme 60.

5′-Deoxy-5-fluorouridine (5′-dFUrd) is a prodrug of 5-fluorouracil (FUra) and has antitumour activity superior to that of the parent drug (FUra) in a variety of model tumour systems. However, research has also demonstrated that 5′-dFUrd was still a relatively poor substrate for uridine phosphorylase, which was attributed to the possibility that uridine phosphorylase could not efficiently cleave the glycosidic linkage to release the FUra under acidic conditions. In view of the fact that the fluorine atom at the 4′-position made the glycosidic linkage of the nucleoside unusually acidlabile, Danenberg and co-workers synthesized the 5′-deoxy-4′,5-difluorouridine **344** as a new prodrug of FUra (Scheme 61).[184] Beginning from 5′-*O*-trityl-5-fluorouridine **341**, the 5′-*O*-methane-sulfonyl derivative **342** was prepared in three steps in 60% yield. Exposure of this compound **342** to KO^{t}Bu in dioxane gave the olefin **343**, which was fluorinated with PhN$^+$(HF)$_x$F$^-$ and subsequently deblocked via catalytic hydrogenation to yield the desired nucleoside **344**.



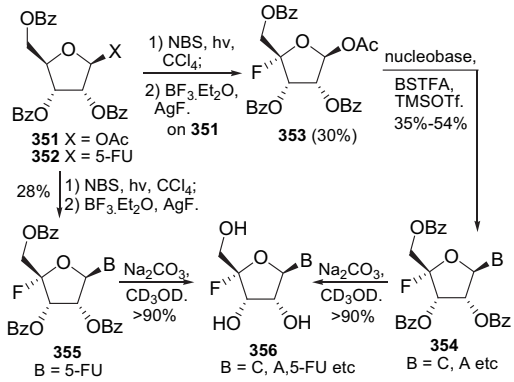
Scheme 61.

In 2001, Jung and Toyota described the synthesis of 2′-deoxy-4′-fluoro thymidines **348** and **350** using a novel method to stereoselectively introduce fluorine into the 4′ position.[185] The *tert*-butyl ester of thymidylic acid **346**, obtained from 2-deoxy-thymidine **345** in six steps and in 67% overall yield, was subjected to NFSI-mediated electrophilic fluorination to predominately afford the β-fluoro-3′-sulfonate **347** in 48% yield (Scheme 62). Reduction of the ester **347** with LiBH$_4$ produced the desired nucleoside **348** in good yield. Utilizing a similar synthetic route, the isomer **350** was also accessed, starting from **349**.



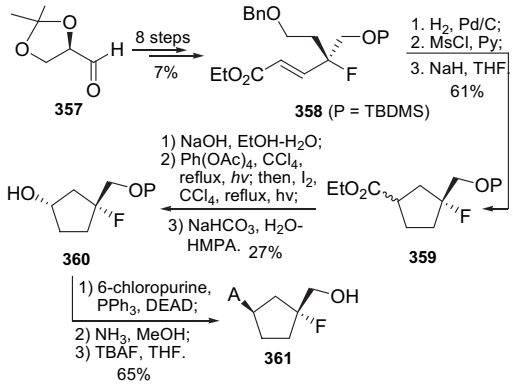
Scheme 62.

In only two-to-three steps via sequential bromination and fluorination of *ribo*-furanoses or nucleosides, Verdine's group described a concise synthesis of 4′-fluoro nucleosides **356** in 2007 (Scheme 63).[186] Their synthesis started with the preparation of 4-fluoro-β-D-*ribo*-furanose **353** via treatment of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose **351** with NBS under a sunlamp followed by direct fluorination of the crude resultant bromide using silver tetrafluoroborate (generated in situ from BF$_3\cdot$Et$_2$O and AgF). Modified Hilbert–Johnson N-glycosylation of furanose **353** with BSTFA and TMSOTf gave the protected 4′-fluoro nucleosides **354** in medium yields. Another alternative approach to 4′-F nucleoside synthesis was achieved through NBS-mediated bromination of 5-FU *ribo*-furanose **352** followed by fluorination with silver tetrafluoroborate and **355** was obtained in 28% yield. The final stage of the 4′-F nucleoside synthesis involved the removal of all the benzoyl groups on the sugar moiety via treatment with methanolic Na$_2$CO$_3$.



Scheme 63.

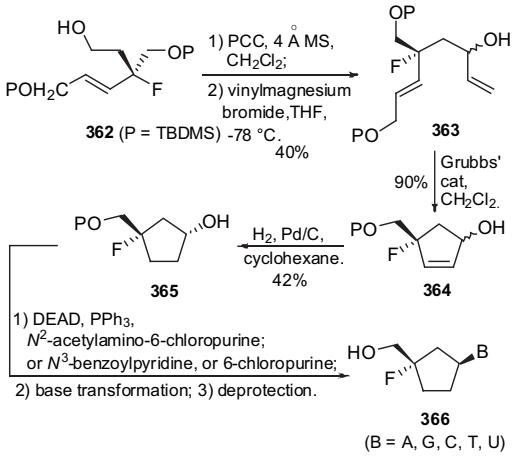
Considering the fact that the carbocyclic nucleoside, abacavir, exhibited a high bioactivity for the treatment of AIDS and that the 4′-fluoro nucleoside, nucleocidin **339**, was a potent inhibitor of protein biosynthesis, Chu's group stereoselectively synthesized the carbocyclic L-4′-fluoro-2′,3′-dideoxyadenosine **361** using an intramolecular nucleophilic substitution reaction as the key step (Scheme 64).[187] In their approach, the key intermediate, *E*-alkene **358**, was first prepared, starting from D-glyceraldehyde **357** in 7% yield and in eight steps based on their own reported route. After hydrogenolysis of **358** followed by mesylation of the resulting alcohol, the generated mesylate was treated with NaH in refluxing THF to yield the enolate intermediate, which simultaneously cyclized to afford the epimeric esters **359** through an intramolecular nucleophilic substitution reaction. Hydrolysis of the esters **359** with NaOH furnished the corresponding acids, which were subjected to oxidative iododecarboxylation followed by hydrolysis to give the α-cyclopentanol **360** as the only product. Coupling of the alcohol **360** with 6-chloropurine under Mitsunobu conditions followed by ammonolysis and deblocking provided the target nucleoside **361** in 65% yield over three steps.



Scheme 64.

Notably, using ruthenium-catalyzed ring-closing methathesis (RCM) as the key step, Chu's group also developed an efficient route to D-4′-fluoro-2′,3′-dideoxynucleosides **366**, starting from the *E*-allylic alcohol **362**, an analogue of the *E*-α,β-unsaturated ester **358** (Scheme 65).[188] After the compound **362** was oxidized by PCC, the resultant aldehyde was subjected to carbonyl addition with

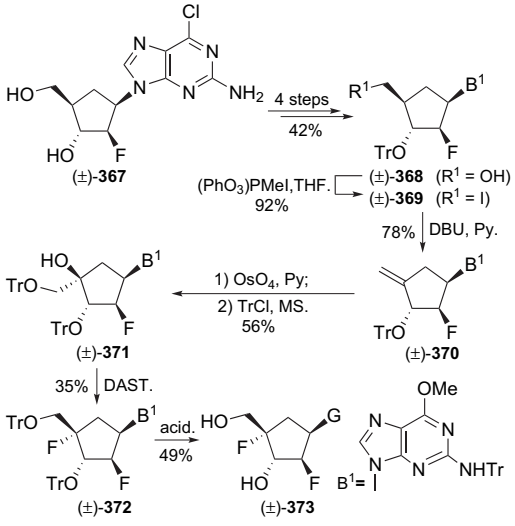
vinylmagnesium bromide to produce the 1,6-dienes **363** in 40% yield, which further underwent an RCM reaction to afford the cyclopentenols **364** in 90% yield. The cyclopentenols **364** were then converted into the cyclopentanol **365** through hydrogenation. The alcohol **365** was condensed with various protected purine or pyrimidine bases followed by ammonolysis and deprotection to give the desired nucleosides **366**.



362 (P = TBDMS)
363
364
365
366
(B = A, G, C, T, U)

Scheme 65.

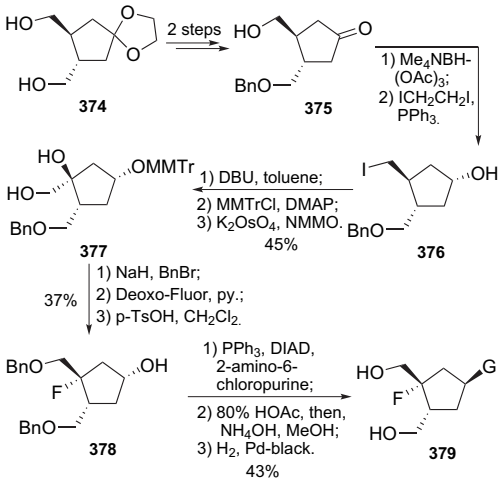
Starting from the carbocyclic 2′β-fluoro-guanosine derivative (±)-**367**, which was an intermediate of synthesizing the carbocyclic nucleoside (±)-**147**,[113] Biggadike and Borthwick presented an entry to the racemic 4′α-fluoro-2′β-fluoro-carbocyclic guanosine (±)-**373**, in 10 steps, in 1990 (Scheme 66).[189] After the compound (±)-**367** was converted, in four steps, into the suitably protected derivative (±)-**368** in 42% overall yield, the reaction of (±)-**368** with a Rhydron reagent gave the iodide (±)-**369**. This compound (±)-**369** was subjected to treatment with DBU to afford the 4′,5′-alkene derivative (±)-**370** in 78% yield. Osmylation of the alkene (±)-**370** and subsequent selective tritylation of the resultant alcohol predominately provided the 4′β-hydroxyl isomer (±)-**371**. Exposure of the compound (±)-**371** to DAST, via an inversion of configuration and in 35% yield, gave the compound (±)-**372**, which was deprotected via acidic treatment to deliver the free nucleoside (±)-**373**.



(±)-**367**
(±)-**368** (R^1 = OH)
(±)-**369** (R^1 = I)
(±)-**370**
(±)-**371**
(±)-**372**
(±)-**373**

Scheme 66.

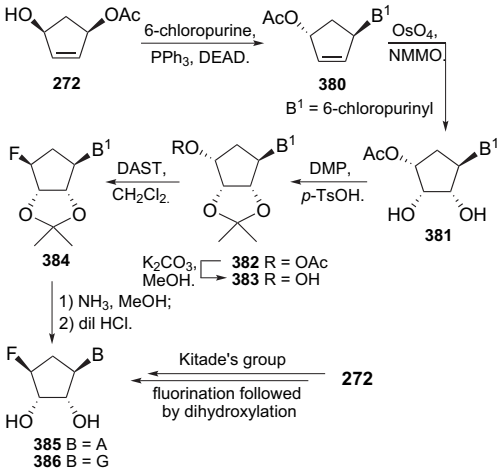
After Borthwick et al. accomplished the synthesis of the 4′-fluorocarbocyclic-2′-deoxyguanosine commencing with the commercially available aristeromycin (carbocyclic adenosine) in over 10 steps and showed that this nucleoside possessed good activities against HSV-1 and HSV-2,[190] the Samuelsson group completed the synthesis of its analogue, 4′-fluorocarbocyclic-2′,3′-dideoxy-3′α-hydroxymethylguanosine **379**, in 1999.[191] In their synthesis (Scheme 67), the cyclopentanol **378** was prepared from the enantiomerically pure (3*S*,4*S*)-bis(hydroxylmethyl)cyclopentanone ethylene glycol ketal **374** in 10 steps involving stereospecific reduction of the keto function of compound **375** and dihydroxylation of the C-4 methylene of **376**. After protection of the primary hydroxyl group in compound **377** with benzyl, replacement of the tertiary C-4 hydroxyl group with fluorine using Deoxo-Fluor as the fluorination reagent and subsequent detritylation using *p*-TsOH in CH_2Cl_2 gave the compound **378**. The desired nucleoside **379** was afforded by coupling of the alcohol **378** with 2-amino-6-chloropurine by a Mitsunobu reaction followed by treatment with HOAc/NH_4OH/MeOH and hydrogenation with Pd-black/H_2.



374
375
376
377
378
379

Scheme 67.

Although some carbocyclic adenosines and aristeromycin were identified as efficient inhibitors of (*S*)-adenosyl-L-homocysteine (AdoHcy) hydrolase,[192,193] a common problem with these compounds that limited their potential usefulness, however, was the associated toxicity arising from their conversion into the corresponding 5′-phosphates.[194–196] In order to circumvent this problem, Schneller's group designed and synthesized the carbocyclic adenosine analogue **385** bearing a fluorine atom at the 4′-position of the cyclopentane ring.[197] Their synthesis began with subjecting

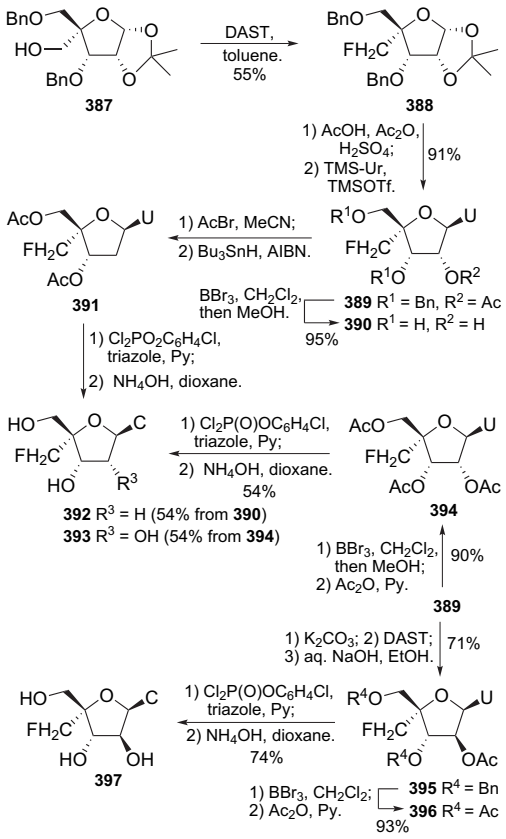


272
380
381
384
385 B = A
386 B = G

Scheme 68.

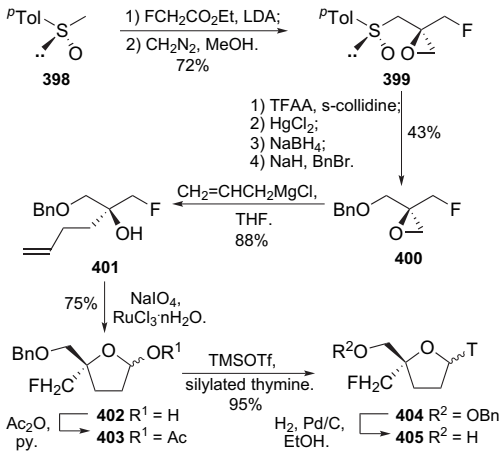
the optically pure monoacetate **272** to a Mitsunobu reaction with 6-chloropurine to afford the 4′α-acetoxy carbocyclic nucleoside **380** (Scheme 68). After dihydroxylation of **380** with OsO_4/NMMO, isopropylidenation of the resultant diol **381** gave the acetate **382**, which was further hydrolyzed with K_2CO_3/MeOH to provide the alcohol **383** in quantitive yield. Fluorination of **383** with DAST gave the fluorinated compound **384.** Treatment of **384** with ammonia and removal of the isopropylidene ketal using dilute HCl finalized the synthesis of the 4′β-fluorinated carbocyclic nucleoside **385**. Interestingly, also using the monoacetate **272** as starting material, Kitade and co-workers recently reported the synthesis of the carbocyclic nucleoside **385** and its guanosine analogue **386**.[198] In contrast to Schneller's strategy of dihydroxylation followed by fluorination, the route of Kitade's group featured the fluorination followed by dihydroxylation.

Based on the fact that some 4′-substituted nucleosides, for example, 4′-azidothymidine, 4′-cyanothymidine and 2′-deoxy-4′-*C*-methylcytidine, exhibited significant and potent anti-HIV and antitumour activities, Kitano and Miura synthesized 4′-*C*-fluoromethylnucleosides **392** and **393** and **397** as potential antineoplastic agents.[199] Their synthesis started from the introduction of fluorine by DAST-mediated treatment of 4-*C*-hydroxylmethyl-D-*ribo*-furanose **387,** and the fluoromethyl compound **388** was provided in 55% yield when toluene was used as the solvent (Scheme 69). Acetolysis of **388** through exposure to $AcOH/Ac_2O/H_2SO_4$ gave the diacetate, which was further subjected to glycosylation with silylated uracil to afford the β anomer **389** as the only product in high yield. Removal of the benzyl groups in the compound **389** provided the 4′-*C*-fluoromethyluridine **390** in 95% yield. Bromination of the triol **390** via reaction with AcBr furnished the 2′-bromo compound, which was reduced by Bu_3SnH/AIBN to yield the 2′-deoxy diacetate **391**. The uracil moiety of **391** was converted into cytosine by the triazole methodology to give the 2′-deoxy-4′-*C*-fluoromethylcytidine **392.** In addition, removal of the dibenzyl groups in the compound **389** followed by acetylation with Ac_2O afforded the triacetate **394** in 90% yield, which was subjected to base transformation to give the 4′-*C*-fluoromethylcytidine **393** in 54% yield. On the other hand, after deacetylation of **389** with K_2CO_3/MeOH, treatment of the resultant alcohol with DAST furnished a *cyclo* compound, which was further hydrolyzed under alkaline conditions to generate the compound **395** in 71% yield over three steps. Removal of the dibenzyl groups in **395** and subsequent acetylation gave the triacetate **396**, which was converted into the deacetylated cytosine derivative **397**, also using the triazole method.



Scheme 69.

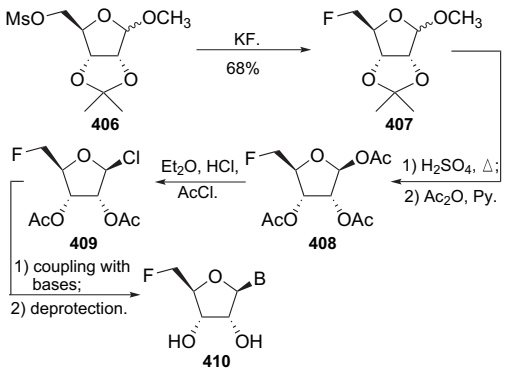
The asymmetric synthesis of enantiomerically pure 4′-fluoromethyl-2′,3′-dideoxythymine was accomplished by Bravo's group in 1994, starting from the commercially available (−)-(*S*)-*p*-tolylmethyl sulphoxide **398**.[200] In their synthesis, acylation of **398** with FCH_2CO_2Et and Pummerer rearrangement were used to get the access to the important intermediate **400** in six steps via compound **399**(Scheme 70). Addition of allylmagnesium chloride to the oxirane **400** proceeded in 88% yield and with high regioselectivity to give the olefin **401**, which was converted into the lactol **402** in 75% yield through oxidation with $NaIO_4/RuCl_3 \cdot nH_2O$. After acetylation of the compound **402**, the resultant acetate **403** was coupled with silylated thymine to yield the 5′-*O*-benzyl-protected nucleoside **404** in 95% yield. Removal of the benzyl group in **404** via hydrogenation gave the targeted nucleoside **405**, which was isolated as the optically pure α anomer and β anomer by flash chromatography. The above methodology provided a convenient entry to many other nucleoside analogues with a great deal of structural diversity at the C-4′ position.



Scheme 70.

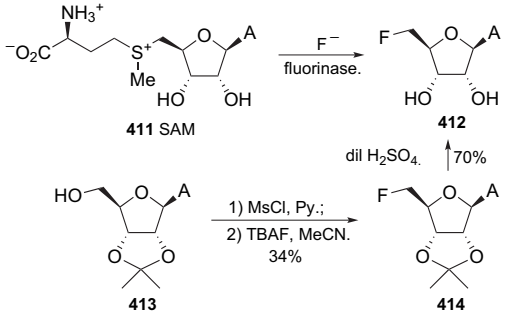
2.5. 5′-Monofluorinated nucleosides

Nucleosides bearing fluorine(s) at C-5′ were designed and synthesized in order to mainly address eliminating the possibility of phosphorylation of these nucleosides to the corresponding mono-, di-, and triphosphates in cells. It was then investigated if these 5′-deoxy-5′-fluoro compounds would show any activities, which would not be dependent on their conversion into the corresponding nucleotides. The synthesis of the 5′-deoxy-5′-fluoro-*ribo*-furanosides **410** was described by Kissman and Weiss in 1958 (Scheme 71).[201] The introduction of the 5′-fluorine was accomplished via treatment of the mesylate **406** with KF to give the fluoromethyl derivative **407** in 68% yield. Acidic hydrolysis of **407** and subsequent acetylation afforded the triacetate **408**, which was converted into the chloro sugar **409** for nucleoside formation. From the key intermediate **409**, a series of nucleosides **410** were obtained through coupling with different purine bases or pyrimidine bases followed by deblocking.



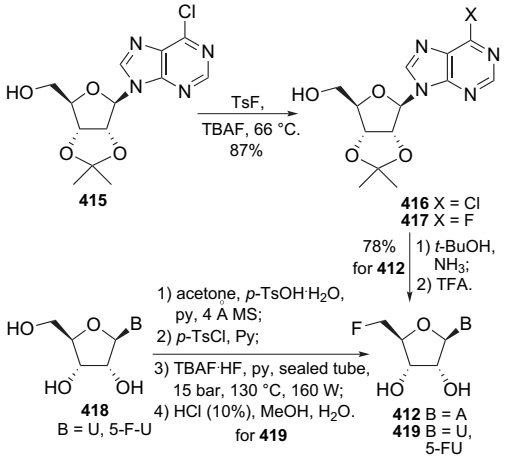
Scheme 71.

In 2002, O'Hagan and co-workers first identified a fluorinase enzyme from *Streptomyces cattleya*, which could mediate and catalyze the conversion of fluoride ion and (*S*)-adenosyl-L-methionine **411** (SAM) into 5′-fluoro-5′-deoxyadenosine **412** (5′-FDA) (Scheme 72).[202] This discovery of O'Hagan et al. opened up a new biotechnological opportunity for the preparation of organofluorine compounds. In the same year, O'Hagan's group also described a simple chemical synthetic route to 5′-FDA **414** in three steps, starting from the ketal-protected adenosine **413**.[203] A further study of **412** as a biosynthetic intermediate during fluorometabolite biosynthesis in *S. cattleya* was also reported later.[204,205]



Scheme 72.

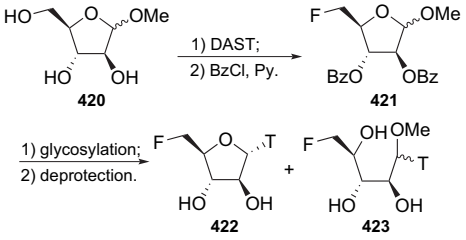
Several years later, an improved synthesis of **412** was described by Scammells and Ashton (Scheme 73).[206] Beginning from the commercially available riboside **415**, fluorination was accomplished by treatment with TsF/TBAF, and a mixture of **416** and **417** was formed in 87% yield. Amination of this mixture followed by deprotection with TFA gave 5′-FDA **412** in 78% yield. Compared with



Scheme 73.

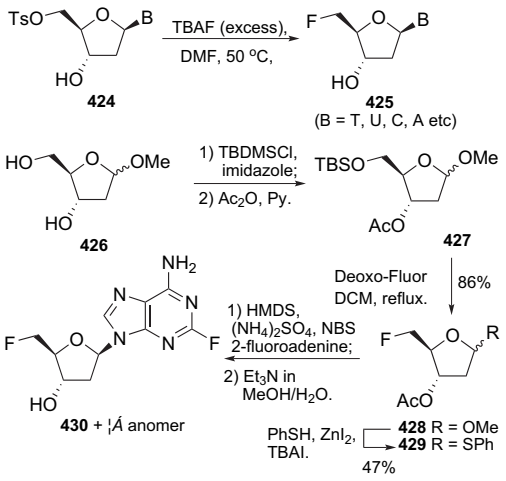
the 24% overall yield of O'Hagan's method, their synthesis highlighted the high yield (68% overall yield). In addition, noteworthy is the recent report of the Phuoc Le group, who utilized a microwave-assisted fluorination approach to obtain 5-deoxy-5-fluoro-substituted uracil nucleoside analogues **419** starting from **418**.[207] By the application of microwaves, the reaction time of the fluorination was significantly reduced.

Designed as an analogue of FLT, 5′-fluoro-α-arabinose nucleoside **422** was available with the triol **420** as the starting material. Introduction of the 5′-fluorine atom was realized via selective fluorination of **420** with DAST (Scheme 74).[208] After protection of the rest of the hydroxyl groups with benzoyl groups was fulfilled, glycosylation of the resultant compound **421** with silylated thymine and subsequent deblocking gave the target nucleoside **422** as the minor product along with the byproduct **423** as the major product.



Scheme 74.

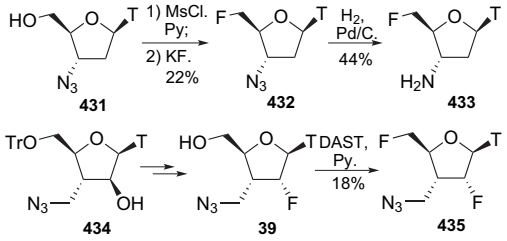
Kowollik and co-workers conveniently addressed the synthesis of 2′,5′-dideoxy-5′-fluoro-*ribo*-nucleosides **425** by treatment of the corresponding 5′-*O*-tosyl nucleoside derivatives **424** with excess TBAF in DMF at 50 °C (Scheme 75).[209] Interestingly, designed as a potent P-site inhibitor of adenylyl cyclase, 2′,5′-dideoxy-2,5′-difluoroadenosine **430** and its α anomer were also synthesised by Kirk's group in 2004.[210] Kirk's synthesis began with the conversion of the methyl 2-deoxy-*ribo*-furanoside **426** to the 3-*O*-acetyl-5-*O*-(*tert*-butyldimethylsilyl) derivative **427** in two steps, and the key steps included the introduction of 5′-fluorine atom through fluorination with bis(2-methoxyethyl)aminosulfur trifluouride (Deoxo-Fluor) and glycosylation of the phenylthioriboside **429** (formed from **428**) with 2-fluoroadenine.



Scheme 75.

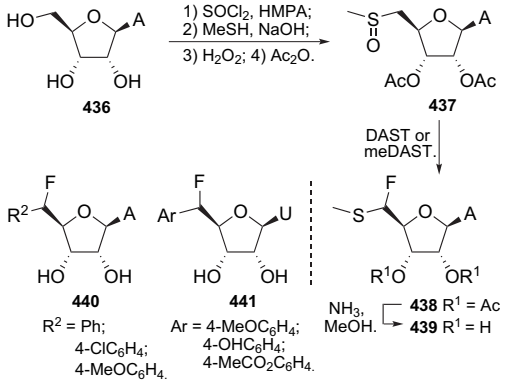
Apart from the 2′,5′-dideoxy-5′-fluoro-*ribo*-nucleosides **425** and **430**, the 2′,3′,5′-trideoxy-3′-azido-5′-fluoronucleoside **432** and 2′,3′,5′-trideoxy-3′-amino-5′-fluoronucleoside **433** were also synthesized using the 3′-azido-3′-deoxythymine **431** as starting material.[211] Mesylation of **431** followed by treatment with KF gave **432**

in 22% yield, which was further subjected to catalytic hydrogenation to provide the 3′-amino analogue **433** in 44% yield (Scheme 76). In addition, starting from the 3′-deoxy-3′-azidomethyl-2′β-hydroxythymidine **434**, 3′,5′-dideoxy-3′-azidomethyl-2′,5′-difluoro-thymidine **435** was also prepared by Munier-Lehmann and co-workers.[67] Due to an undesired intramolecular attack of the 2-carbonyl of the thymine on the 5-*O*-diethylaminosulfur difluoride intermediate, fluorination of the intermediate **39** with DAST afforded the target compound **435** in only 18% yield.



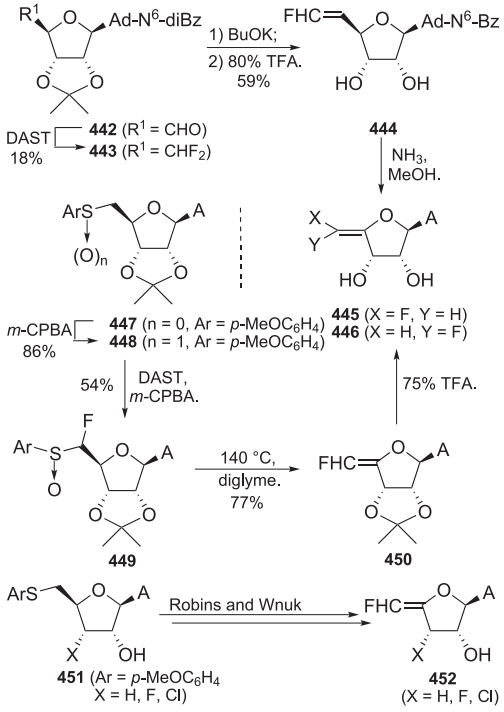
Scheme 76.

Designed as an analogue of 5′-deoxy-5′-(methylthio)adenosine (MTA), which has been demonstrated to be a potent inhibitor of bovine liver AdoHcy hydrolase, 5′-deoxy-5′-fluoro-5′-(methylthio)adenosine **439** was synthesized by Sufrin's group in 1989[212] and further evaluated for inhibitory activity towards MTA phosphorylase and for its biological effects in L120 and L5178Y murine leukaemia cell lines. After a four-step conversion of adenosine **436** into the MTA sulfoxide derivative **437** (Scheme 77), fluorination was accomplished through treatment with (dimethylamino)sulfur trifluouride (meDAST) or DAST to provide the 5′-fluorinated diacetate **438**, which was further subjected to deacetylation with NH_3/MeOH to give the desired nucleoside **439**. Later, using a similar synthetic route, Robins and co-workers described an access to other analogues, 5′-aryl-5′-fluoro-5′-thioadenosine **440**[213] and 5′-aryl-5′-fluoro-5′-thiouridines **441**,[214] starting from their corresponding thioethers or sulfoxides using DAST/$SbCl_3$ or XeF_2 as the fluorinating reagent.



Scheme 77.

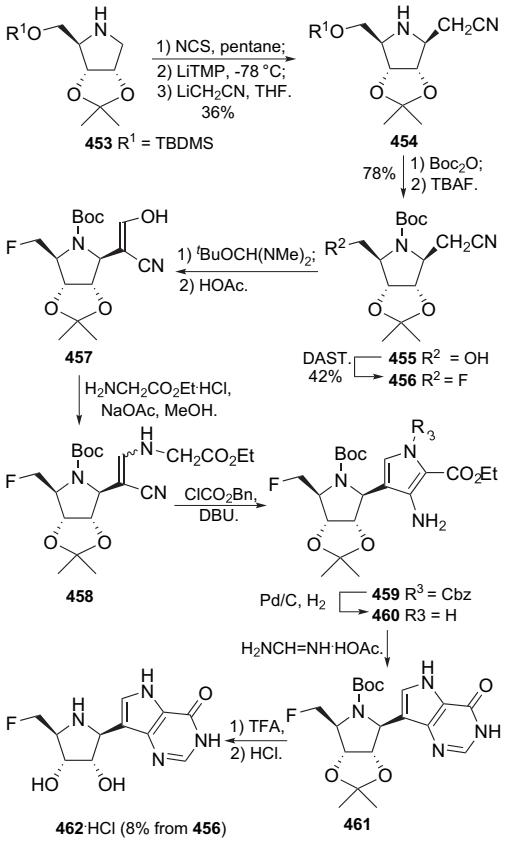
Based on the enzymatic pathway for the conversion of *S*-adenosyl-L-homocysteine (SAH) into adenosine, McCarthy, Prakash et al. designed, synthesized and biologically evaluated a novel class of mechanism-based inhibitors of SAH hydrolase, the 4′,5′-unsaturated 5′-fluoroadenosine nucleosides **445** and **446**.[215] They developed two different routes to address the synthesis of **445** and **446** (Scheme 78). The key steps in the first method included the fluorination of the 2,3-*O*-isopropylideneadenosine-5-aldehyde derivative **442** with DAST in 18% yield and dehydrofluorination of the compound **443** with BuOK in DMSO. Removal of the protecting group in **444** with NH_3/MeOH finalized the synthesis of **445** and **446**. Alternatively, after isopropylideneadenosine was converted into the thioether **447**, oxidation with *m*-CPBA to **448** and subsequent fluorination produced the α-fluoro sulfoxide **449** in 47% yield, which was further transformed into the desired nucleosides **445** and **446** by means of thermolysis followed by deprotection of **450** with TFA. In addition, starting from 3′-deoxy- and 3′-(chloro and fluoro)-3′-deoxyadenosines **451**, three other 4′,5′-unsaturated 5′-fluoroadenosine nucleoside analogues **452** were also synthesized by Robins and Wnuk et al. using a similar route to the second method of McCarthy's group.[216]



Scheme 78.

In 2000, Evans et al. described the synthesis of 5′-deoxyfluoro-aza-C-nucleoside **462**, which was designed as a potential transition-state analogue inhibitor for purine nucleoside phosphorylase.[217] Their synthesis started from the iminoribitol derivative **453**, which was converted into the cyanomethyl C-glycoside derivative **454** by the addition of lithiated acetonitrile to imine intermediate (Scheme 79). After protection of the compound **454** with Boc and desilylation with TBAF to form **455**, the 5′-fluorine atom was introduced with DAST to afford the 5-deoxy-5-fluoro derivative **456** in 42% yield. Installation of the 9-deazahypoxanthin-9-yl base from the acetonitrile moiety was achieved in 8% overall yield and in seven steps, of which the important steps included treatment of the compound **456** with a Bredereck reagent, reaction of the enol **457** with ethyl glycinate, exposure of the ester **458** to DBU/$ClCO_2Bn$ to give **459** and coupling of the pyrrole **460** with formamidine acetate to produce **461**.

Very recently, 5′-fluoro-5′-deoxyaristeromycin **472** was synthesized in Schneller's group, based on the rationale of well-documented beneficial biological consequences of a fluoro-for-hydroxyl exchange. The important synthetic procedure was a Mitsunobu coupling of 4-fluoromethylcyclopentan-1-ol derivative **470** with N^6-bis-Boc-protected adenine to give **471** (Scheme 80).[218] The intermediate **470** was prepared from ribose **463** in a straightforward fashion. Conversion of **463** into the aldehyde **464** was accomplished in 54% total yield over three steps including selective cyclopentylidenation, iodination and BuLi-mediated ring opening/deletion. A Grignard reaction of **464** with CH_2=CHMgBr gave the alcohol **465**, which was subjected to RCM followed by oxidation to

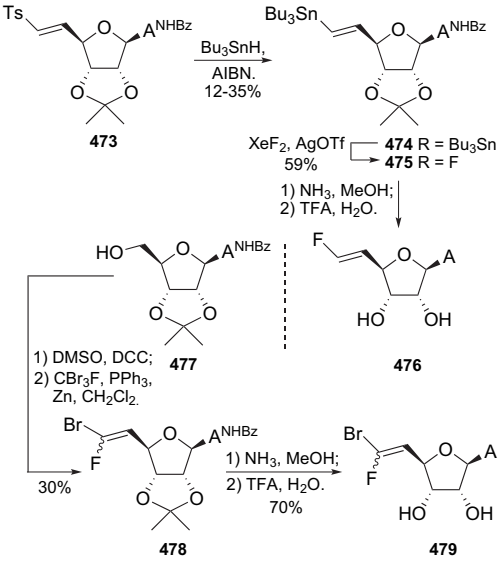


Scheme 79.

afford the ketone **466**. 1,4-Addition of compound **466** with CH_2=CHMgBr and subsequent reduction with $LiAlH_4$ yielded the alcohol **467** in 62% yield. After protection of the hydroxyl group with PMB, transformation of the vinyl group in **468** into a hydroxymethyl group was realized via scission oxidation with $NaIO_4$ and reduction with $NaBH_4$. Fluorination of the primary alcohol **469** with DAST and removal of the PMB group using DDQ gave the precursor **470** of the Mitsunobu reaction. Schneller's procedure is adaptable to prepare a number of 5′-fluoro-5′-deoxycarbocyclic analogues with diversity in the heterocyclic base.

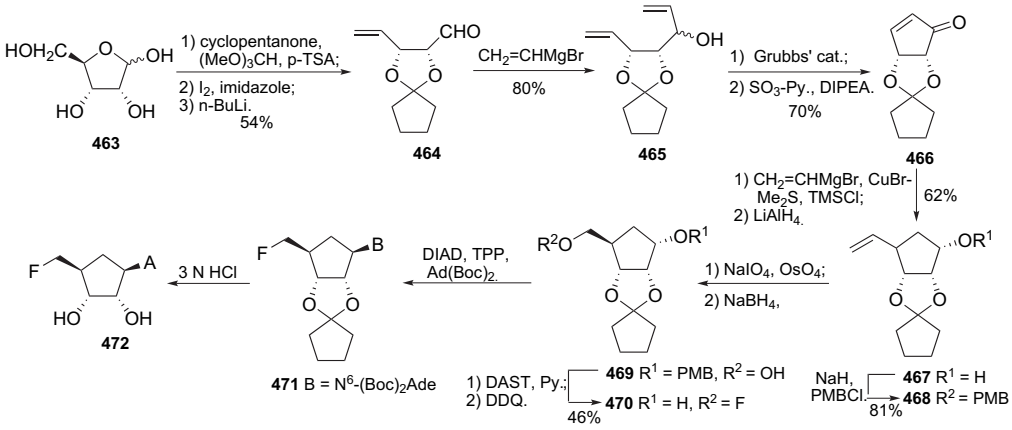
2.6. 6′-Monofluorinated nucleosides

Designed as potential mechanism-based inhibitors against AdoHcy hydrolase and as antiviral reagents, Robins' group synthesized the 6′-fluorohomovinyl adenosine derivative **476** and the 6′-bromo-6′-fluorohomovinyl adenosine derivative **479** (Scheme 81).[219,220] The synthesis of the 6′-fluorohomovinyl nucleoside **476** commenced with the conversion of the starting material, 6′-(*E*)-vinyl sulfone homonucleoside **473**, into the vinyl 6′-stannane **474** via treatment with Bu_3SnH/AIBN. Fluorodestannylation of the compound **474** with XeF_2/AgOTf gave the protected 6′-fluoride **475**, which was further subjected to deprotection to provide the (*E*)-5′,6′-didehydro-6′-deoxy-6′-fluorohomoadenosine **476**. With the protected adenosine **477** as the starting material, synthesizing the 6′-bromo-6′-fluorohomovinyl nucleoside **479** involved Moffatt oxidation, treatment of the resultant 5′-carboxaldehyde with '(bromofluoromethylene)triphenylphosphorane' reagent and deprotecton of the compound **478**.

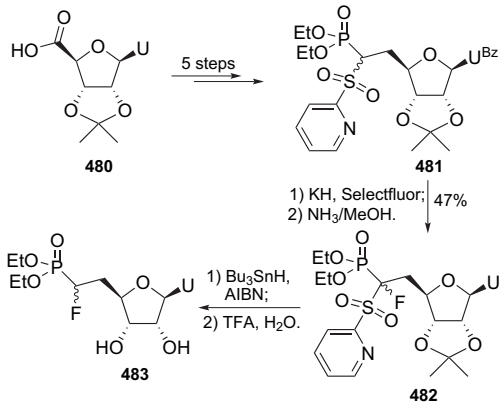


Scheme 81.

Aside from the 6′-fluorohomovinyl derivative **476** and the 6′-bromo-6′-fluorohomovinyl derivative **479**, Robins and Wnuk also first synthesized the 6′-deoxy-6′-fluorohomonucleoside 6′-phosphonate **483** using their developed methodology, which highlighted the stannyl radical-mediated cleavage of π-deficient heterocyclic sulfones.[221] In their synthesis, 2′,3′-*O*-isopropylideneuridine 5′-carboxylic acid **480** was converted into the pyridin-2-yl sulfone **481** in five steps, and this was subjected to fluorination with Selectfluor followed by debenzoylation to yield the α-fluoro sulfone phosphonate **482** in 47% yield (Scheme 82). Exposure of **482** to Bu_3SnH/AIBN



Scheme 80.



Scheme 82.

caused the cleavage of the sulfonyl linkage, and further removal of the isopropylidene group afforded the target nucleoside phosphonate **483**. Their methodology provided a facile new route for the preparation of α-fluoro-α-[$^{2/3}$H] carbonyl compounds and phosphonates.

Based on the fact that some carbocyclic adenosine analogues have been shown to be the inhibitors of AdoHcy hydrolase,[14,222,223] especially after aristeromycin and neplanocin A had been reported to exhibit strong activities against vaccinia virus and potent inhibitory activities for AdoHcy hydrolase with a K_i of 5 and 8 nM, respectively (Fig. 6),[193,224–227] several groups synthesized a series of fluorinated analogues of aristeromycin and neplanocin A. In 1988, Prisbe and co-workers synthesized and biologically evaluated 6′-fluorinated aristeromycin (±)-**487** and (±)-**490** (Scheme 83).[228] Their synthesis started from the epoxy diol (±)-**484**. After the functionalized (±)-**485** was prepared using their reported procedure, the fluorine atom was introduced via a nucleophilic substitution reaction to give the compound (±)-**486**. (±)-6′β-Fluoroaristeromycin **487** was delivered from (±)-**486** in several steps, which involved the reduction of the azide **486**, elaboration of the 9-adeninyl substituent and final deprotection. On the other hand, after monotritylation of the epoxy diol (±)-**484**, reversing the configuration of the C-6 hydroxyl group was realized via a nucleophilic substitution reaction and the epimeric alcohol (±)-**488** was provided in 36% yield. Trifluoromethanesulfonation of the compound (±)-**488** and subsequent reaction with TBAF furnished the (±)-α-fluoro epoxide **489** in 74% yield. The compound **489** was converted into (±)-6′α-fluoroaristeromycin **490** through treatment with adenine in the presence of K_2CO_3 followed by deprotection. It should be pointed out that, three years later, Roberts and co-workers developed a convenient route to the optically pure epoxy diol **484** by hydrolysis of a diester compound using porcine pancreatic lipase as catalyst.[229]

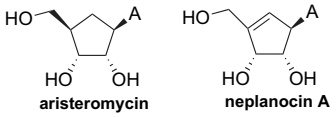
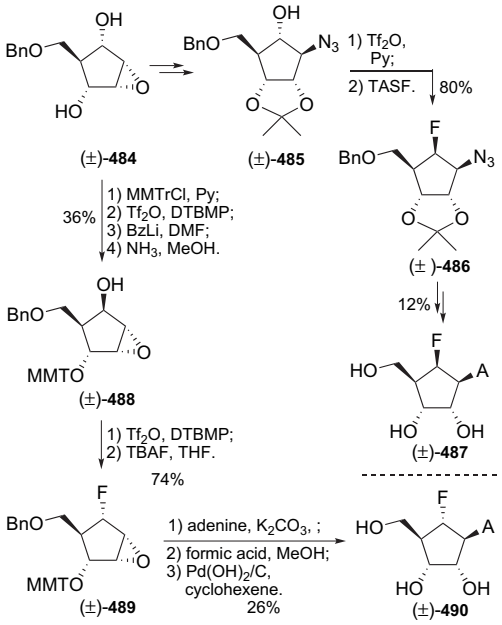
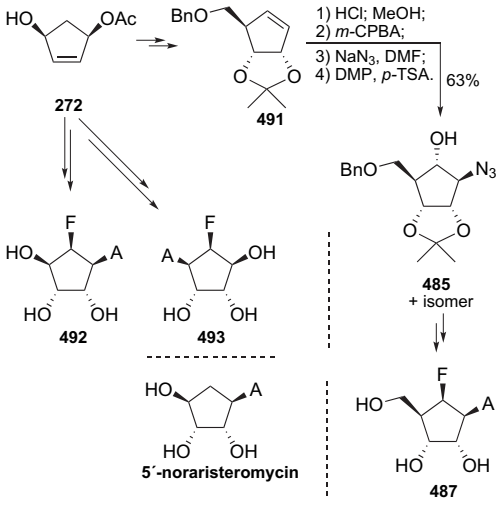


Figure 6. Structures of aristeromycin and neplanocin A.

Schmeller and Yin reported the chiral synthesis of 6′β-fluoroaristeromycin **487** in 2005.[230] Their synthesis was built upon (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate **272**, which was converted into the cyclopentene **491** in a straightforward fashion (Scheme 84). Subjecting **491** to the sequence of deisopropylidenation, epoxidation, sodium azide ring opening and re-isopropylidenation gave the azide **485** along with its isomer. Using the same procedure as that described by Prisbe et al.,[228] the target nucleoside 6′β-fluoroaristeromycin **487** was provided. As an



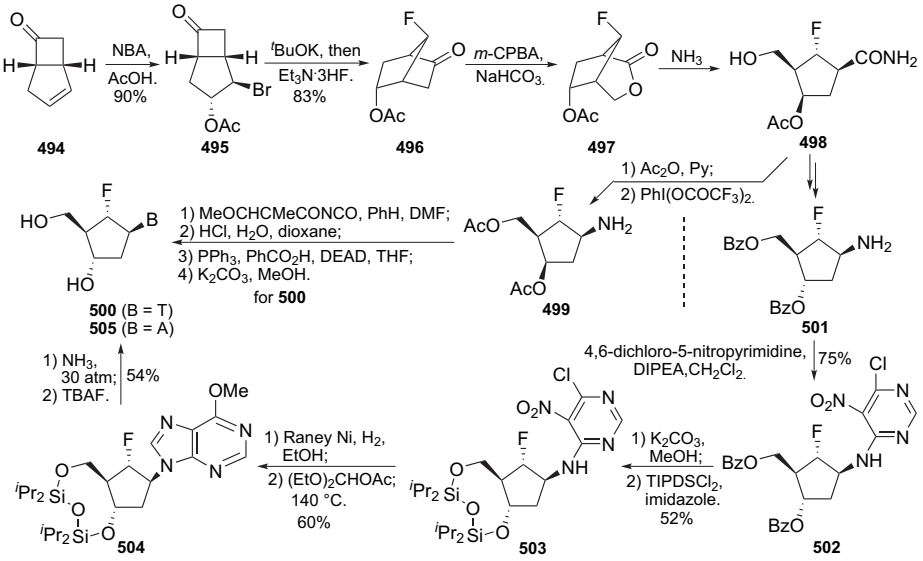
Scheme 83.



Scheme 84.

extension of their work, the 5′-noraristeromycin fluoro analogue **492** and its enantiomer **493** were also synthesized from **272** in view of the fact that 5′-noraristeromycin has been a source of new antiviral candidates.

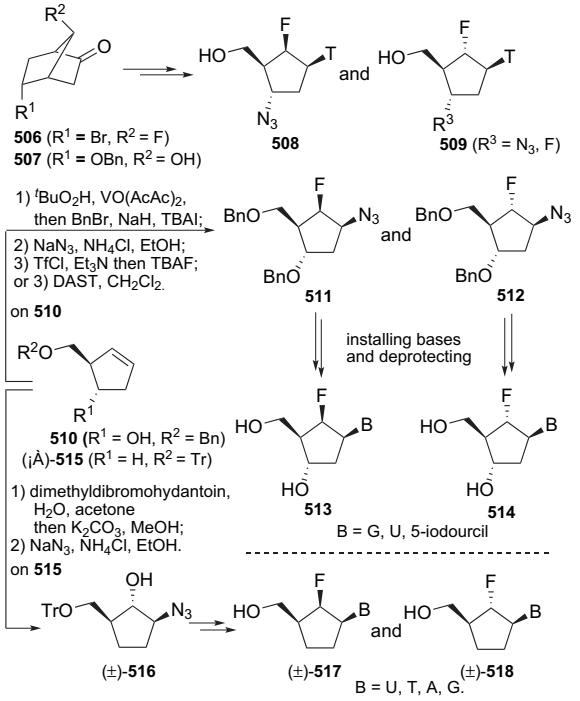
The synthesis of the 6′-fluorocarbocyclic nucleosides **500** and **505** has been addressed by Roberts et al., starting from the bicyclic ketone **494**, in 16 and 2% overall yield, respectively.[231] As the important step of their synthesis, the optically active ketone **494** reacted with NBA/AcOH to produce the bromoacetate **495** in 90% yield, which was treated with ^{t}BuOK followed by $Et_3N\cdot 3HF$ to give the fluoroester **496** in 83% yield (Scheme 85). Subjecting **496** to Baeyer–Villiger oxidation afforded the lactone **497** as the main isomer, which was further treated with liquid ammonia to give the ring-opening product **498**. After acetylation of the compound **498**, the resultant diacetate was transformed into the amine **499** using the Hofmann–Loudon strategy. Installation of a thymine base from the amine group in the compound **499** followed by Mitsunobu inversion and hydrolysis furnished the target carbocyclic nucleoside **500**. On the other hand, after the compound **498** was converted into the amine **501** using Mitsunobu inversion and the



Scheme 85.

modified Hofmann reaction as the key steps, coupling with 4,6-dichloro-5-nitropyrimidine provided the dibenzoate **502**, which was converted into the compound **503** once the protecting groups were replaced. Reduction of the nitro group in **503** via hydrogenation over Raney nickel followed by cyclization of the resultant amine product using diethoxymethyl acetate by heating afforded the purine **504** in 60% yield, from which the synthesis of the 6′-fluorocarbocyclic nucleoside **505** was finalized after ammonolysis and fluoride-mediated desilylation.

Besides the 6′-fluorocarbocyclic nucleosides **500** and **505**, Roberts et al.[232,233] also completed the synthesis of the other 6′-fluorocarbocyclic nucleosides **508** and **509** using a similar strategy to that described above. Their synthesis started from the intermediates **506** and **507**, two analogues of the fluoroester **496** (Scheme 86). In addition, the synthesis of the 6′-fluorocarbocyclic



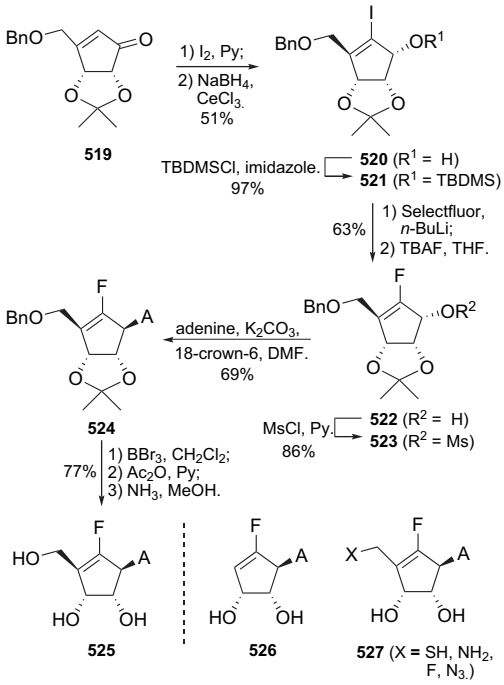
Scheme 86.

nucleosides **513** and **514** was also accomplished by the same group using another synthetic route. This route featured the conversion of the chiral cyclopentene derivative **510** into the fluoro azides **511** and **512** in three steps, which included Sharpless asymmetric epoxidation, NaN_3-mediated ring opening and DAST-mediated fluorination or nucleophilic substitution fluorination (Scheme 86).[234,235] Roberts and co-workers also carried out the synthesis of 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides (±)-**517** and (±)-**518**, starting from the racemic trityl derivative (±)-**515**,[236] which was subjected to epoxidation and NaN_3-mediated ring opening to afford the azido-alcohol (±)-**516**. After DAST-mediated fluorination or nucleophilic substitution fluorination of the alcohol (±)-**516**, the nucleosides (±)-**517** and (±)-**518** were delivered through installation of the different bases from the azide moiety.

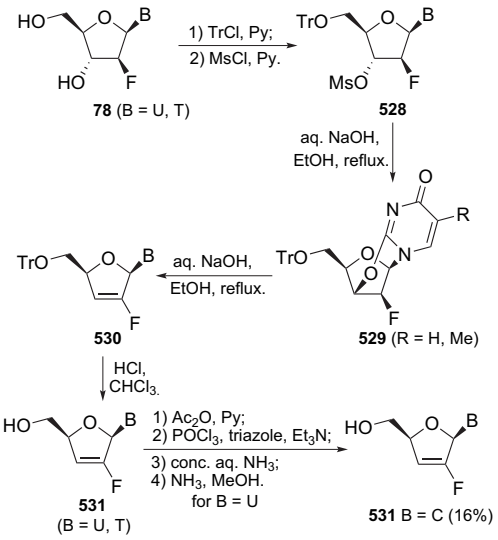
In 2003, Jeong's group synthesized fluoroneplanocin A **525** and found that **525** exhibited twofold more potent SAH inhibitory activity than the parent, neplanocin A (Fig. 6).[237] Their synthesis commenced with the cyclopentenone derivative **519**, which was firstly converted into its iodide **520** through iodination and subsequent Luche reduction (Scheme 87). After protection of the alcohol **520** as the silyl ether, treatment of the compound **521** with Selectfluor/*n*-BuLi followed by TBAF-mediated desilylation provided the fluoro derivative **522** in 63% yield. Mesylation of **522** gave compound **523** in 86% yield, which was condensed with the adenine anion to generate the protected nucleoside **524**. Deprotection of **524** yielded the target product **525** in 77% yield. In addition, the fluorinated cyclopentenyladenine **526**[238] and 5′-substituted fluoroneplanocin A analogues **527**[239] were also prepared and biologically evaluated by this group.

2.7. 2′-/3′-Monofluoro-2′,3′-unsaturated nucleosides

2′,3′-Didehydro-2′,3′-unsaturated nucleosides have played a major role in the development of antiviral agents, especially anti-AIDS agents.[240,241] Among this class of compounds, d4T,[242,243] L-d4C,[244,245] L-d4FC[244,245] and abacavir[246,247] have been regarded as the most interesting therapeutic candidates for anti-HIV therapy, because of their potent antiviral activities. Introduction of a fluorine atom at the 2′-position of dideoxypurine nucleosides is well known to stabilize the glycosyl bond.[81,248] Currently, agents containing the 2,3-unsaturated sugar moiety with fluoro substitution have become rational targets in the search for safe, effective, and chemically stable antiviral agents. Thus, it was of interest to



Scheme 87.



Scheme 88.

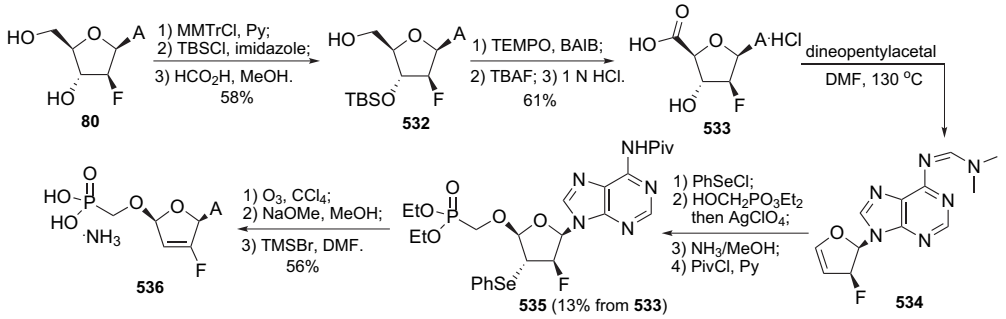
synthesize 2- or 3-fluoro-2,3-unsaturated nucleosides, which could result in significant biological activity.

In 1990, Martin and co-workers first reported the synthesis of 2′,3′-dideoxy-2′,3′-didehydro-2′-fluoronucleosides **531** (B=U, T, C).[94] Their synthesis started from the conversion of 2′-deoxy-2′-fluoro-*arabino*-furanosylpyrimidine nucleosides **78** (B=U, T) into the compounds **528** through tritylation and subsequent mesylation (Scheme 88). After a brief treatment of **528** with aqueous NaOH, the resultant anhydronucleosides **529** were further treated with aqueous NaOH to furnish the protected 2′,3′-dideoxy-2′,3′-didehydro-2′-fluoronucleosides **530**. Removal of the trityl group with HCl in $CHCl_3$ gave the target nucleosides **531** (B=U, T). In addition, the cytosine nucleoside **531** (B=C) was also obtained through the base conversion. A biological assay showed that the nucleoside **531** (B=C) exhibited medium antiviral activity with an IC_{50} value of 10 μM.

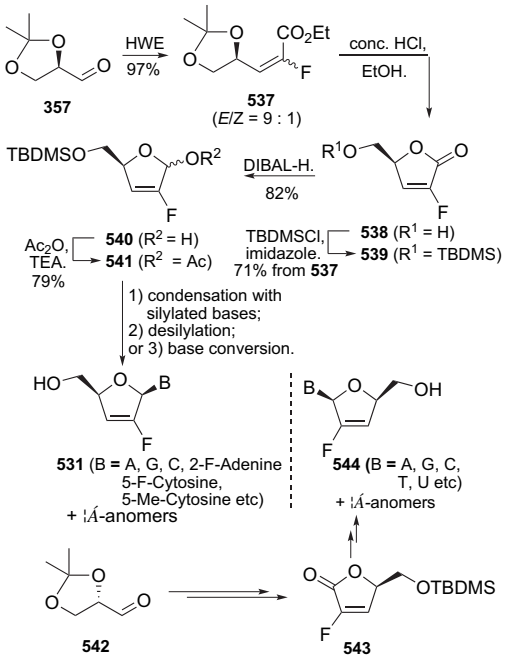
Starting from the fluorinated adenosine nucleoside **80**, Boojamra's group fulfilled the synthesis of the 2′,3′-dideoxy-2′,3′-didehydro-2′-fluoro nuelcoside derivative **536**, a novel nucleoside phosphonate RT inhibitor (Scheme 89).[249] Firstly, a sequential protection/deprotection sequence on **80** allowed access to the alcohol **532**. Oxidation of **532** and removal of the TBS group with TBAF followed by treatment with 1 N HCl gave the salt **533** in 61% overall yield. After conversion into the glycal **534** via the reaction of **533** with dineopentylacetal, treatment with PhSeCl, $AgClO_4$-mediated glycosylation with $HOCH_2PO_3Et_2$ and subsequent conversion of the protecting group produced the 4′-β-phosphonomethoxy-3′-α-phenylselenide isomer **535**. Finally, O_3-mediated oxidation–elimination of compound **535** followed by deprotection provided the target phosphonic acid **536** as a monoammonium salt. Some modified purine analogues of compound **536** were also synthesized by Boojamra et al.[250]

Interestingly, Chu and co-workers developed a novel efficient route to the 2′,3′-dideoxy-2′,3′-didehydro-2′-fluoro-D-nucleosides **531** (B=A, G, C, etc.) (Scheme 90).[251] The key point of their synthetic strategy involved the preparation of the important intermediate **541**, starting from 2,3-*O*-isopropylidene-D-glyceraldehyde **357** in five steps. An HWE reaction between the compound **357** and $(Et_2O)_2P(O)CHFCO_2Et$ gave the *E*-isomer **537** as the main product, which was transformed into the 2-fluorobutenolide intermediate **538** via acidic removal of the isopropylidene ketal and simultaneous cyclization. After protecting the alcohol **538** as its silyl ether, reduction of the resultant lactone **539** yielded the lactol **540** in 82% yield. Acetylation of **540** gave the key intermediate **541** in 79% yield, which was subjected to condensation with the various silylated bases (purine, pyrimidine) and subsequent TBAF-mediated desilylation and (or) base conversion to afford the target nucleosides **531** (B=A, G, C, etc.). In addition, this group have also synthesized the L-isomers **544** (B=A, C, T, U, etc.), beginning from the L-glyceraldehyde derivative **542**, using a similar synthetic route (via **543**).[252,253]

Besides the Chu group's method, another route to the 2′,3′-dideoxy-2′,3′-didehydro-2′-fluoro-L-nucleosides **544** (B=T, A, 5-I-

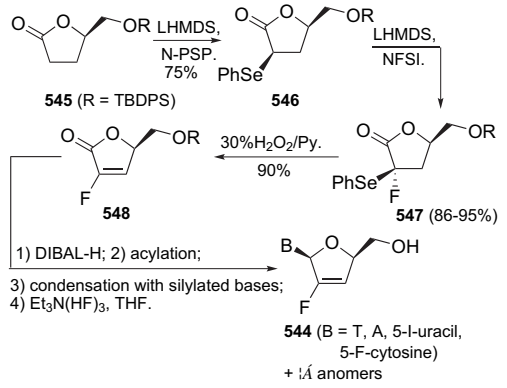


Scheme 89.



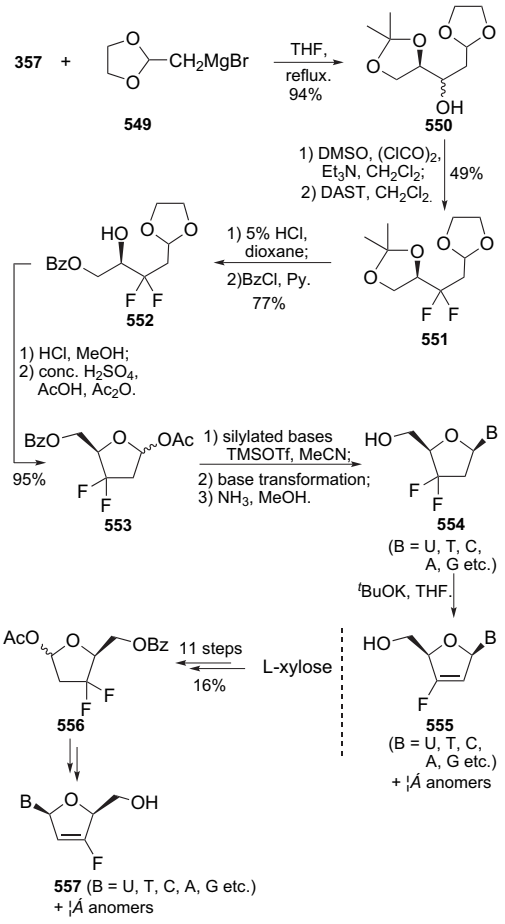
Scheme 90.

uracil, 5-F-cytosine) was also developed by Chen's group.[254] The noteworthy points of this new route included the stereospecific introduction of a phenylseleno moiety into the lactone **545** through treatment with LHMDS/*N*-(phenylseleno)phthalimide (*N*-PSP) and subsequent stereoselective fluorination of **546** with NFSI (Scheme 91). Oxidative elimination of the phenylseleno moiety in **547** afforded the enone lactone **548** in 90% yield, which, in a straightforward fashion, was converted into the L-nucleosides **544** after reduction with DIBAL-H, acylation, glycosylation with silylated bases and $Et_3N(HF)_3$-mediated desilylation.



Scheme 91.

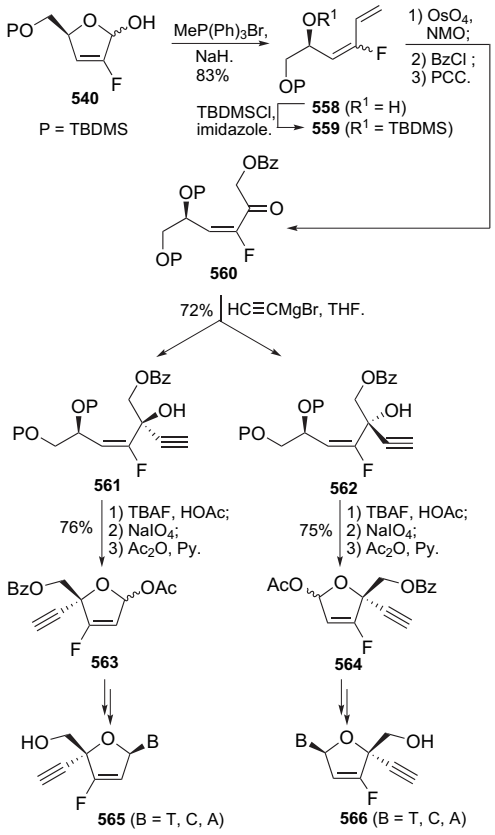
Additionally commencing with 2,3-*O*-isopropylidene-D-glyceraldehyde **357**, Chu's group accomplished the synthesis of 2′,3′-didehydro-2′,3′-dideoxy-3′-fluoro-β-D-nucleosides **555** (Scheme 92).[255] After reaction of the compound **357** with (1,3-dioxolan-2-ylmethyl)magnesium bromide **549** in refluxing THF, a Swern oxidation of the resultant alcohol **550** gave the corresponding ketone, which was fluorinated by DAST to generate the difluorinated intermediate **551**. Compound **551** was subjected to selective deprotection and subsequent benzoylation to produce the alcohol **552**. Conversion of the intermediate **552** into the epimeric acetate **553** was accomplished by treatment with HCl/MeOH followed by concentrated H_2SO_4/AcOH/Ac_2O. Coupling of the key intermediate **553** with the various persilylated bases gave the protected nucleoside derivatives, which, after debenzoylation and (or) base transformation, were converted into the *gem*-difluorinated nucleosides **554**. Exposure of the free nucleosides **554** to ^{t}BuOK in THF resulted in the target nucleosides **555**. It should be noted that, after preparing the key intermediate **556** starting from L-xylose in 11 steps and 16% overall yield, this group also pursued the synthesis of 2′,3′-dideoxy-3′-fluoro-β-L-nucleosides **557** using a similar strategy.[256,257]



Scheme 92.

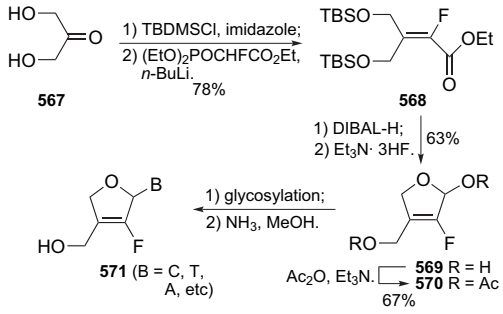
In 2004, Chu and co-workers also described an entry to the 2′,3′-didehydro-2′,3′-dideoxy-4′-ethynyl-3′-fluoro D- and L-furanosyl nucleosides **565** and **566**, starting from the intermediate **540**.[258] Treatment of the lactol **540** with $MeP(Ph)_3Br$/NaH gave the diene **558**, which was silylated to provide the the fully protected compound **559** (Scheme 93). After selective dihydroxylation of the terminal double bound in the diene **559**, the resultant anomeric diol was converted into the α,β-unsaturated ketone **560** through selective benzoylation of the primary hydroxyl and subsequent oxidation. A Grignard reaction between the ketone **560** and HC≡CMgBr afforded a separable mixture of **561** and **562** in 72% yield. The diastereoisomers **561** and **562** were subjected to desilylation with TBAF, oxidation with $NaIO_4$ and acetylation to provide the furanose derivatives **563** and **564**, respectively. The target nucleosides **565** and **566** were afforded after glycosylation of the furanose diastereoisomers **563** and **564** with silylated bases and debenzoylation, respectively.

Based on a bioisosteric rationale, Jeong and co-workers synthesized the 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro apionucleosides **571**,[259] which combined the properties of 2′,3′-didehydro-2′,3′-dideoxy nucleosides and apionucleosides. In their synthesis, 1,



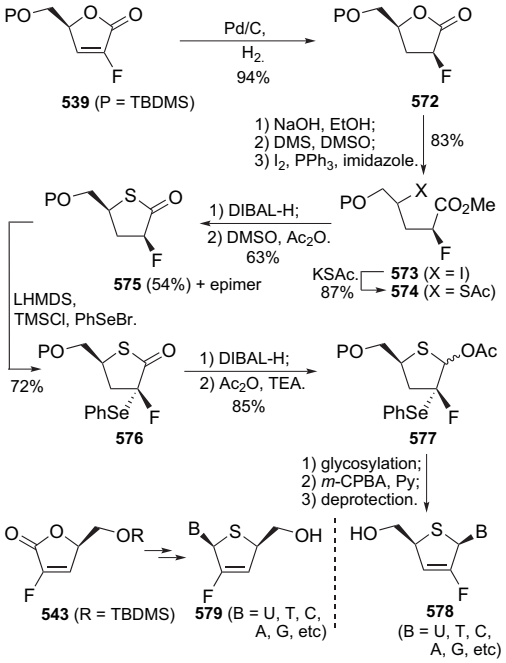
Scheme 93.

3-dihydroxyacetone **567** was firstly protected as the disilyl ether, which was further subjected to a Horner–Emmons reaction to afford the fluoroester **568**. Reduction of **568** with DIBAL-H gave the corresponding aldehyde, which, after desilylation with $Et_3N\cdot 3HF$, was transformed into the lactol **569** via a simultaneous cyclization (Scheme 94). After diacetylation of the diol **569**, the apionucleoside analogues **571** were obtained through coupling of the resultant compound **570** with silylated base followed by deprotection.



Scheme 94.

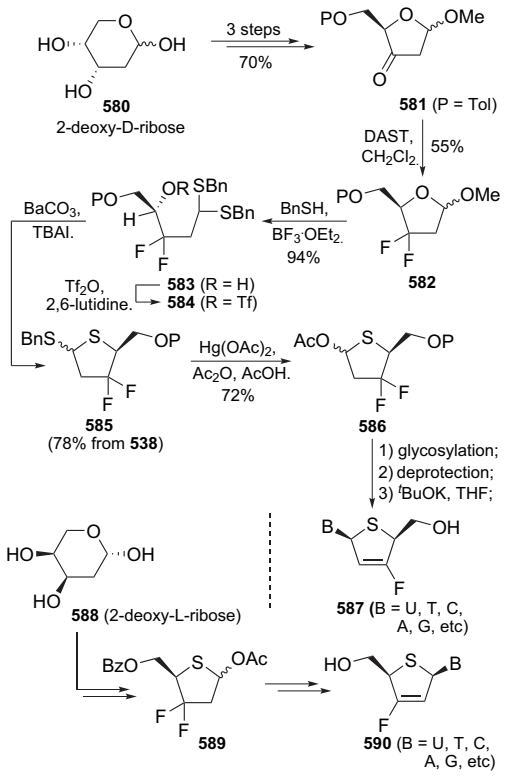
Aside from the aforementioned 2′- or 3′-fluoro-2′,3′-didehydro-2′,3′-dideoxy-furanosyl nucleosides, their corresponding thionucleosides and carbocyclic nucleosides were also synthesized by the Chu group and by Toyota's group. Chu and co-workers realized the synthesis of the 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro-4′-thio-D-nucleosides **578**, starting from the lactone **539**. After the lactone **539** was hydrogenated in 94% yield, the resultant compound **572** was converted into the iodoester **573** in three steps and 83% overall yield (Scheme 95).[260] Subjecting **573** to nucleophilic attack by KSAc gave an epimeric mixture of the thioacetates **574** in 87% yield. Reduction of the compound **574** and a subsequent Moffat-type oxidation afforded the thiolactone **575** along with its epimer. Treatment of the compound **575** with LHMDS/TMSCl/PhSeBr resulted in the stereoselective introduction of a phenylselenyl group into the C-2 position. DIBAL-H reduction of the resultant 2-fluoro-2-phenylselenothiolactone **576** followed by acetylation provided the key intermediate, the β-D-*ribo*-furanoside derivative **577**, from which the target thionucleosides **578** were afforded via glycosylation with various pyrimidine or purine bases followed by *m*CPBA-mediated elimination and deprotection. By means of a similar strategy, the nucleosides **579** with an L-configuration were also prepared from the lactone **543**.[261,262]



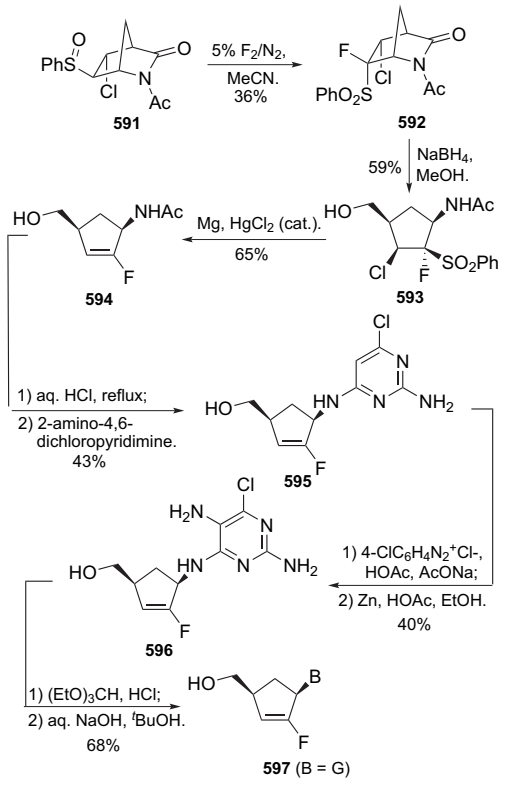
Scheme 95.

Access to 2′,3′-didehydro-2′,3′-dideoxy-3′-fluoro-4′-thio-L-nucleosides **587** was developed, starting from the ketone **581**, which was prepared from the 2-deoxy-D-ribose **580** in three steps and 70% overall yield (Scheme 96).[263] Exposure of the ketone **581** to DAST gave the difluorinated intermediate **582** in 55% yield, which was subjected to a ring-opening reaction with $BnSH/BF_3\cdot Et_2O$ to afford the thioacetal **583**. After **538** was converted into the triflate **584**, cyclization to the thiosugar **585** was accomplished through treatment with $BaCO_3$/TBAI. Reaction of the compound **585** with $Hg(OAc)_2/Ac_2O$ in acetic acid delivered the transglycosylated compound **586** in 72% yield, glycosylation of which followed by deprotection and ^{t}BuOK-mediated elimination provided the target L-nucleosides **587**. In addition, the D-isomer nucleosides **590** were also prepared utilizing similar reaction conditions, starting from 2-deoxy-L-ribose **588** via the *gem*-difluorinated intermediate **589**.[263]

In 1998, Toyota's group completed the synthesis of the 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro-D-carbocyclic nucleoside **597** (B=G). Their synthesis featured α-fluorination of the 6-phenylsulfinyl-2-azabicyclo[2.2.1]heptan-3-one **591** with 5% F_2/N_2, and the fluorinated product **592** was formed in 36% yield (Scheme 97).[264] Reductive amide-bond cleavage of the compound **592** with $NaBH_4$ gave the amide **593** in 59% yield, which was further treated with $Mg/HgCl_2$ (cat.) in EtOH to afford the fluoroalkene **594** in 65% yield. Usual installation of the purine ring from **594** provided the desired carbocyclic nucleoside **597** in several steps, which included treatment with 10% aqueous HCl followed by coupling with 2-amino-



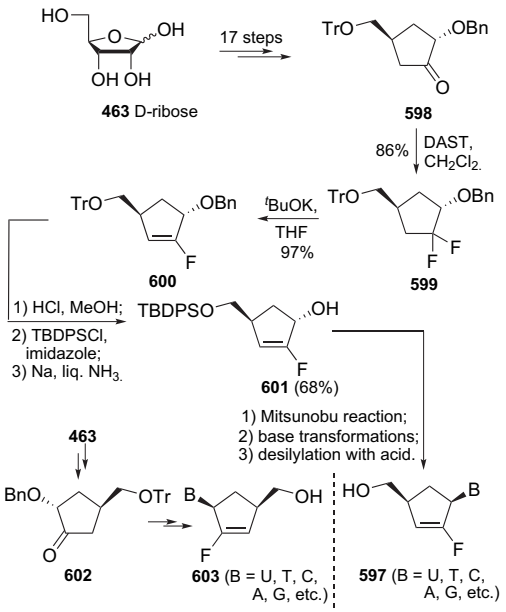
Scheme 96.



Scheme 97.

4,6-dichloropyridimine, diazotization of compound **595** using 4-$ClC_6H_4N_2^+Cl^-$ followed by reduction with Zn/HOAc, ring closure of the compound **596** with $(EtO)_3CH$ under acidic conditions and subsequent alkaline hydrolysis.

Interestingly, Chu and co-workers recently developed another route to the 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro-D-carbocyclic nucleoside **597**.[265] In their synthetic route, the key intermediate **598** was obtained, starting from D-ribose **463** in 17 steps (Scheme 98). After fluorination of the ketone **598** with DAST, the resultant *gem*-difluorinated compound **599** was furnished in 86% yield. Subsequent treatment of **599** with ^{t}BuOK in THF gave the cyclic allylic alcohol derivative **600**, which was converted into the cyclic α-fluoro allylic alcohol **601** in three steps, involving removal of the trityl group, silylating with TBDPS and debenzylation using Na/liq. NH_3. Installation of the bases was carried out through a Mitsunobu reaction between the compound **601** and various bases, and the target nucleosides **597** were delivered after deprotection and base transformations. The synthesis of the L-isomeric nucleosides **603** was also addressed from D-ribose via the intermediate **602** using similar reaction conditions.

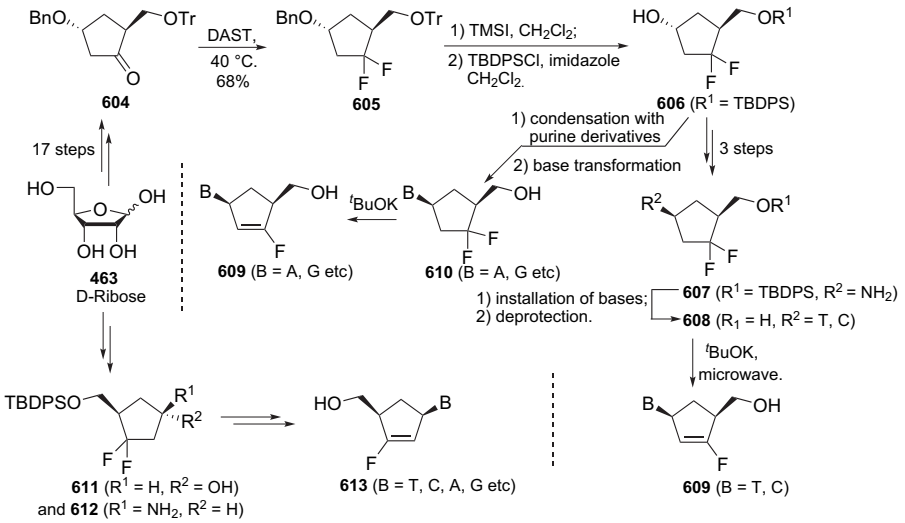


Scheme 98.

Besides the 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro-carbocyclic nucleosides **597** and **603**, Chu's group also fulfilled the synthesis of D- and L-2′,3′-didehydro-2′,3′-dideoxy-3′-fluoro-carbocyclic nucleosides **609** and **613** (Scheme 99).[266] Their synthesis commenced with conversion of the D-ribose **463** into the keto compound **604** in 17 steps, which was further fluorinated with DAST to afford the difluoro compound **605** in 68% yield. Removal of all the protecting groups in **605** followed by selective protection generated the key intermediate **606**, which was further converted into the amine **607** in three steps. The pyrimidine nucleosides **609** (B=T, C) were obtained via installation of pyrimidine bases from the amine group in compound **607** and subsequent microwave-assisted elimination reactions of **608**. Condensation between the alcohol **606** and purine base derivatives gave access to the difluoronucleosides **610**, from which the target purine nucleosides **609** (B=A, G, etc.) were furnished through elimination reactions. Using similar procedures, the D-series nucleosides **613** were also prepared from the intermediates **611** and **612**.

3. Difluorinated nucleosides

The *gem*-difluoromethylene (CF_2) group has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen.[267] Analogues of di- and triphosphates in which the CF_2 groups have

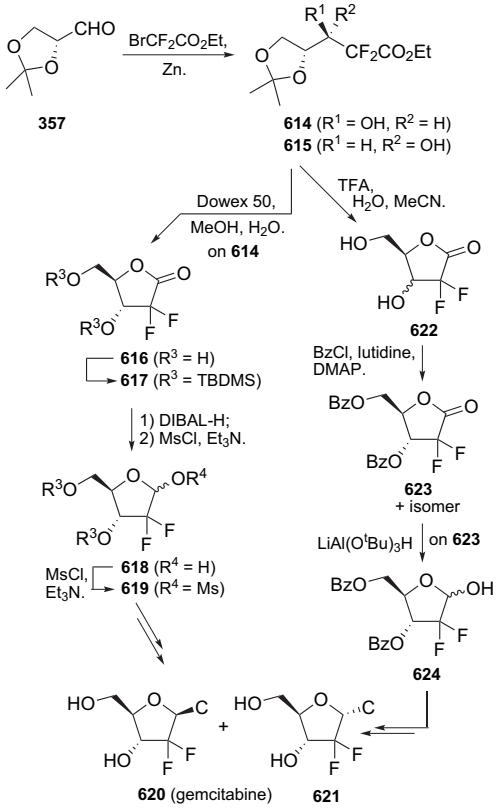


Scheme 99.

replaced the pyrophosphate oxygen have been used as substrates in enzymatic reactions.[268–271] Thus, the CF_2 group was extensively used to modify not only nucleotides, but also nucleoside analogues. For example, important work on 2,2-difluoro-2-deoxyriboses and the corresponding nucleosides has resulted in the discovery of gemcitabine (2′,2′-difluorodeoxycytidine; Gemzar), an inhibitor of RDPR that was launched in 1996. Gemcitabine has been shown to be highly active against cancer and has been approved for treating several types of tumour.[33–42] Gemcitabine, after metabolic phosphorylation, not only inhibits RDPR, but also interacts with other enzymes involved in DNA biosynthesis, which have resulted in its superior efficiency. The high antiviral and antineoplastic activities of gemcitabine reveal the special influence of the CF_2 group on the biological activities of nucleosides. Thus, a number of nucleosides containing a CF_2 group on the sugar moiety have been synthesized and biologically evaluated.

3.1. *gem*-Difluorinated furanyl nucleosides

Originally, gemcitabine was prepared from the 2,2-difluoro-2-deoxyribose **614**, itself available from the addition of the Reformatsky reagent of $BrCF_2CO_2Et$ on the 2,3-*O*-isopropylidene glyceraldehyde **357** (Scheme 100).[33] Removal of the isopropylidine group resulted in simultaneous cyclization, and the resultant lactone **616** was further silylated to afford the product **617**. After conversion of the compound **617** into the mesylate **619**, condensation with persilylated cytosine provided gemcitabine **620** and its α anomer **621**. In view of the fact that this synthetic route needed separation of the isomers **614**/**615** and **620**/**621** by HPLC, Chou et al. improved the method by utilizing the same synthetic route, but selecting Bz over TBDMS as the protecting group for the hydroxyl groups in the compound **616**.[272] Once this modification had been made, three distinct improvements were available. First and foremost, crystallization of the desired ribonolactone **623** from a diastereomeric mixture consisting of **623** and its isomer was easily realized. Besides, the ratio of the desirable β-isomer **620** against the α-isomer **621** was increased to 1:1 from 1:4, which was afforded when TBDMS was used as the protecting group. Finally, crystallization of the gemcitabine **620** from a 1:1 anomeric mixture was also accomplished. In addition, starting from the lactol **618** and the lactone **623**, a series of other *gem*-difluorinated nucleoside analogues were also synthesized and biologically evaluated.[273–275] It should be noted that the Castillón group, in 1998, developed an efficient strategy to synthesise the intermediate, 2-deoxy-3,5-di-*O*-benzoyl-

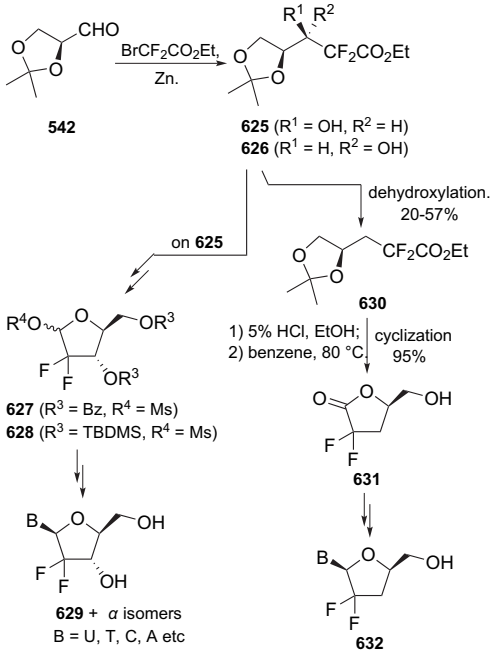


Scheme 100.

2,2-difluoro-D-ribose **618** (R^3=R^4=H), from D-glucose or D-mannose and further offered another formal synthesis of gemcitabine.[276]

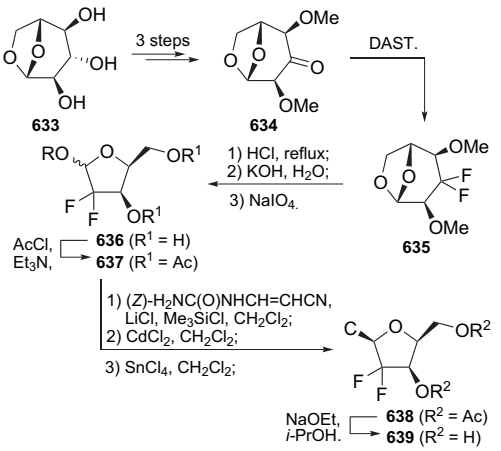
In view of the high bioactivities of gemcitabine, Chu's group synthesized 2′-deoxy-2′,2′-difluoro-L-*erythro*-pentofuranosyl nucleosides, the L-counterpart analogues of gemcitabine.[277] Commencing with (*S*)-2,3-*O*-isopropylidene glyceraldehyde **542**, their synthetic strategy was almost identical to that of gemcitabine (Scheme 101). After preparation of the key intermediates **627** and **628** from the alcohol **625**, coupling with various persilylated pyrimidines, 6-chloropurine or silylated 2-amino-6-chloropurine followed by standard procedures provided the 2′-deoxy-2′,2′-difluoro-L-*erythro*-pentofuranosyl nucleosides **629** along with the

α anomers. Additionally, starting from a mixture of diastereoisomers **625** and **626**, this group also described the entry to a series of 2′,3′-dideoxy-2′,2′-difluoro-L-*glycero*-pentofuranosyl nucleosides **632** with dehydroxylation and subsequent cyclization of compound **630** as the important steps (Scheme 101).[278] Besides, Chu and co-workers also made access to a series of L-2′,3′-dideoxy-3′,3′-difluoronucleosides and D-2′,3′-dideoxy-3′,3′-difluoronucleosides **603** available during their synthesis of D- and L-2′,3′-didehydro-2′,3′-dideoxy-3′-fluoronucleosides.[255–257]



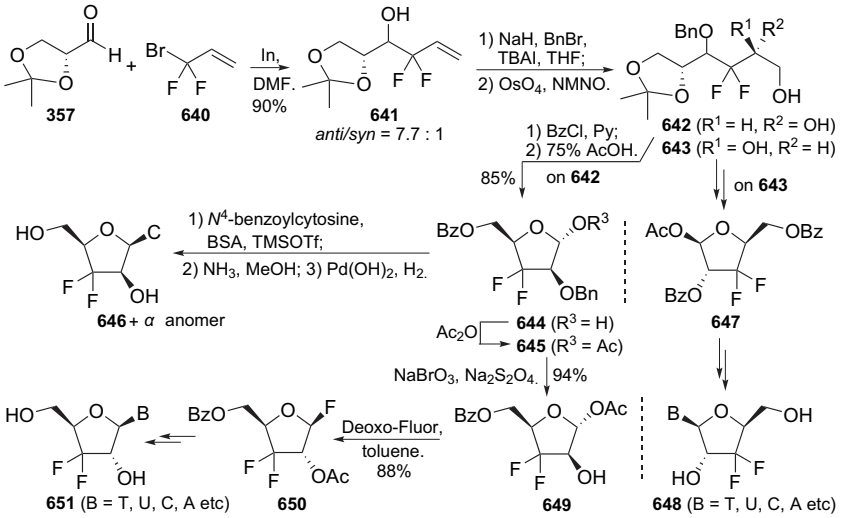
Scheme 101.

The synthesis of 2′-deoxy-2′,2′-difluoro-β-nucleocytidine **639** was developed by Chen in 2003.[279] The process started from the 1,6-anhydro-β-L-glucopyranose **633**, which was first converted into the ketone **634** through three-step simple transformations of functional groups (Scheme 102). After difluorination of the compound **634** with DAST, the resultant *gem*-difluoromethylated derivative **635** was subjected to acidic hydrolysis and oxidation with $NaIO_4$ to yield the lactol **636**. Acetylation of **636** provided the acetate **637**. Condensation of the compound **637** with (*Z*)-$H_2NC(O)NHCH{=}CHCN$ and subsequent removal of the protecting group from **638** with NaOEt provided the target nucleoside **639**. A simple process and a high output rate were the advantages of the synthetic route.



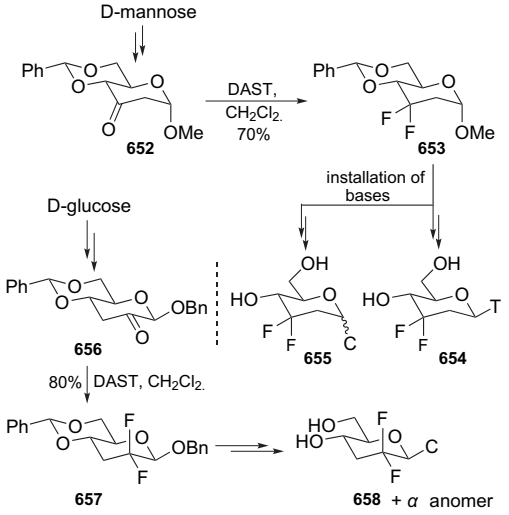
Scheme 102.

In 2003, Qing and co-workers completed the synthesis of D- and L-3′-deoxy-3′,3′-difluoronucleosides **646** and **648**.[280,281] Their synthesis featured the indium-mediated reaction of 1-(*R*)-glyceraldehyde acetonide **357** and 3-bromo-3,3-difluoropropene **640**, and the difluorohomoallyl alcohol **641** was afforded in 90% yield and 77% de (Scheme 103). Protection of the hydroxyl group in **641** followed by Os-catalyzed dihydroxylation gave the separable diols **642** and **643**, which were further subjected to a series of simple transformation of protecting groups to furnish the furanoses **645** and **647**, respectively. Coupling of the acetates **645** and **647** with silyated bases and subsequent removal of the protecting group gave the target nucleosides **646** and **648**, respectively. In addition, the Qing group also accomplished the synthesis of D-β-3′-deoxy-3′,3′-difluoronucleosides **651**, starting from the intermediate **645**, which was subjected to debenzylation with $NaBrO_3/Na_2S_2O_4$ to give **649**. Treatment of **649** with Deoxo-Fluor accidentally yielded the compound **650**.[281] Condensation of the α-fluoro derivative **650** with the various bases followed by deprotection gave the desired nucleosides **651** as the β anomers.



Scheme 103.

In view of the high bioactivities against cancer cells of gemcitabine, Castillón and Fernández synthesized 2′,3′-dideoxy-3′,3′-difluoro and 2′,3′-dideoxy-2′,2′-difluoropyranosyl nucleosides, analogues of gemcitabine (Scheme 104).[282] In their synthesis, D-mannose and D-glucose were converted into the protected ketones **652** and **656**, respectively. After *gem*-difluorination of the ketones **652** and **656** with DAST, the resultant difluorinated derivatives **653** and **657** were subjected to glycosylation followed by deblocking to give the desired nucleosides **654**, **655** and **658**, respectively.



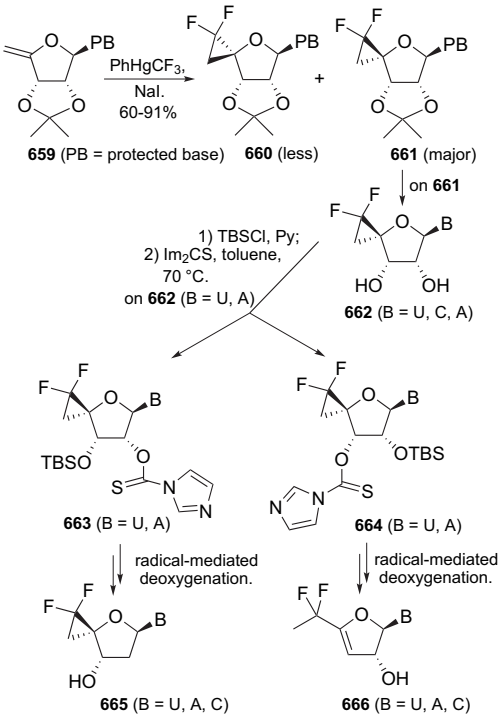
Scheme 104.

Recently, a synthetic route to 4′-(2,2-difluorospirocyclopropane) analogues of adenosine, cytidine and uridine was described by Robins and Nowak (Scheme 105).[283] Their synthesis featured the addition of difluorocarbene (generated in situ from $PhHgCF_3$/NaI) to the 4′,5′-unsaturated nucleoside derivatives **659**, and the diastereomeric mixtures of the 2,2-difluorospirocyclopropane adducts **660** and **661** were afforded in 60–91% yield. Removal of all the protecting groups in the main isomer **661** and (or) further base transformation gave the free 4′-(2,2-difluorospirocyclopropane) nucleoside analogues **662.** In addition, the 2′-deoxy nucleoside analogues **665** and 4′-(1,1-difluoroethyl)-3′,4′-unsaturated nucleoside derivatives **666** were also prepared through the stannyl radical-mediated deoxygenation of 3′-*O*-TBS-2′-thionocarbamate derivatives **663** and 2′-*O*-TBS-3′-thionocarbamate derivatives **664**, respectively, which were prepared from the nucleosides **662** (B=U, A) in two steps.

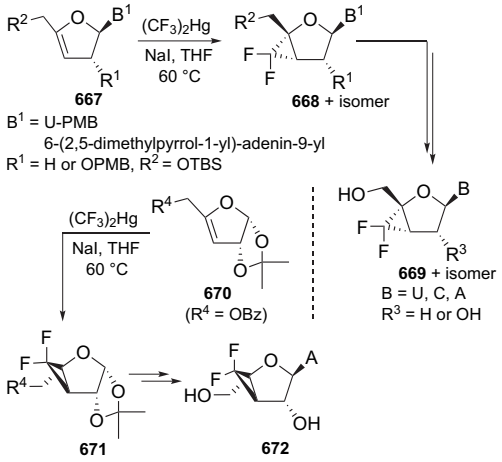
Besides the 2,2-difluorospirocyclopropane nucleosides **665**, Robins and co-workers recently accomplished the synthesis of the difluoromethylene-bridged nucleoside analogues **669** and **672**, also utilizing difluorocarbenation of the suitably premodified 3′,4′-unsaturated analogues **667** and **670** as the key steps (difluorocarbene was generated from $(CF_3)_2Hg$/NaI/THF) (Scheme 106).[284,285] The stereoselectivities of the difluorocarbenation reactions depended on the steric hindrance of the C=C bond environment. The crystal structures of some difluoromethylene-bridged nucleosides were also investigated by this group.

3.2. *gem*-Difluorinated thio-/aza-/carbocyclic nucleosides

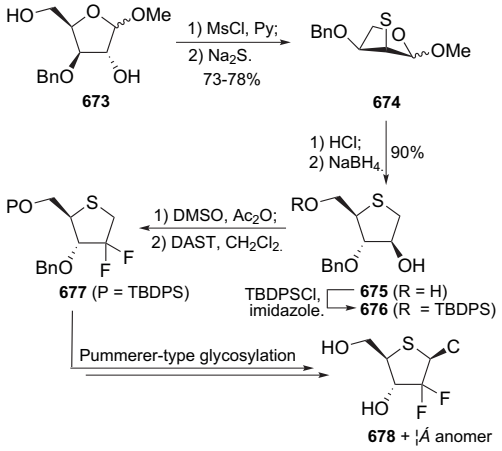
Based on the fact that 3′-thiocytidine (3TC) and gemcitabine have been well documented as highly active antitumour agents, Yoshimura et al. synthesized 4′-thiogemcitabine **678** and its α anomer in 1996.[286,287] After preparing 1-*O*-methyl-3-*O*-benzylxylose **673** from D-glucose, Yoshimura and co-workers first achieved access to the bicyclic compound **674** in good yield via treatment with MsCl/pyridine followed by Na_2S/DMF (Scheme 107). Acidic hydrolysis and



Scheme 105.



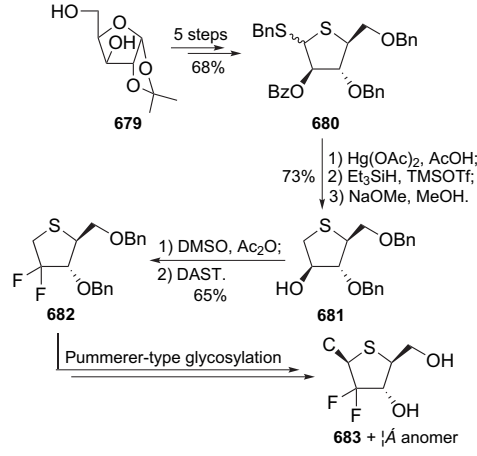
Scheme 106.



Scheme 107.

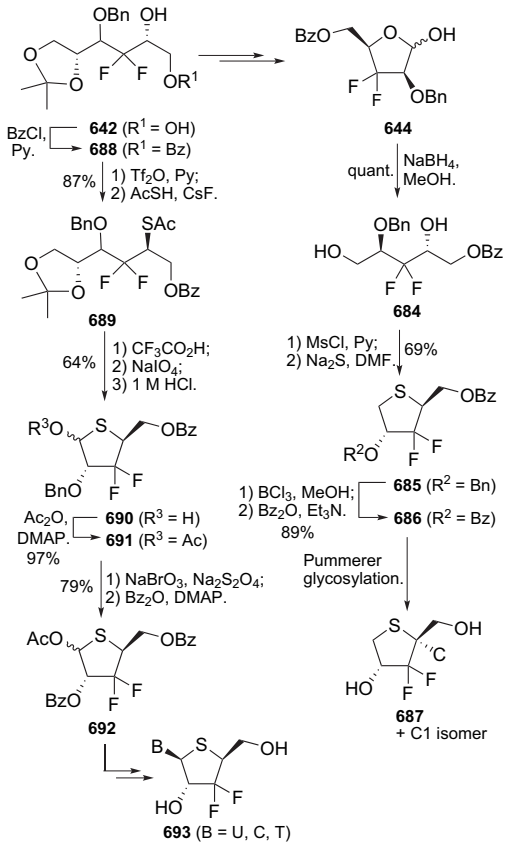
subsequent hydride reduction of compound **674** produced the 1,4-anhydro-4-thioarabinitol **675** in 90% yield. Protection of the primary alcohol in **675** with TBDPS followed by oxidation of the secondary hydroxyl in **676** gave the corresponding 2-keto derivative, which was further fluorinated with DAST to afford the 2-deoxy-2,2-difluoro derivative **677**. After transformation of the 3′-protecting group, a Pummerer-type glycosylation was used to synthesize the desired 4′-thiogemcitabine **678** and its α anomer.

Considering the fact that D-β-4′-thiogemcitabine **678** exhibited weak antineoplastic activity and some L-series nucleosides have been shown to be highly active against solid tumours, Jeong's group, in 1998, developed a short and efficient route to the synthesis of the L-2′-deoxy-2′,2′-difluoro-4′-thionucleoside **683**, the enantiomer of the D-nucleoside **678**.[288] Their synthesis started from the commercially available, 1,2-isopropylidene-D-xylose **679**, which was converted into the thiosugar **680** in 68% overall yield over five steps (Scheme 108). Reaction of the compound **680** with $Hg(OAc)_2$/AcOH followed by treatment of the resultant acetate with Et_3SiH/TMSOTf and subsequent removal of a benzyl group with NaOMe/MeOH gave the key intermediate **681** in 73% yield. Oxidation of the compound **681** and fluorination of the generated ketone with DAST provided the *gem*-difluoromethylated derivative **682**. The compound **682** was further subjected to Pummerer glycosylation and removal of the protecting groups to give the L-2′-deoxy-2′,2′-difluoro-4′-thionucleoside **683** and its α anomer.



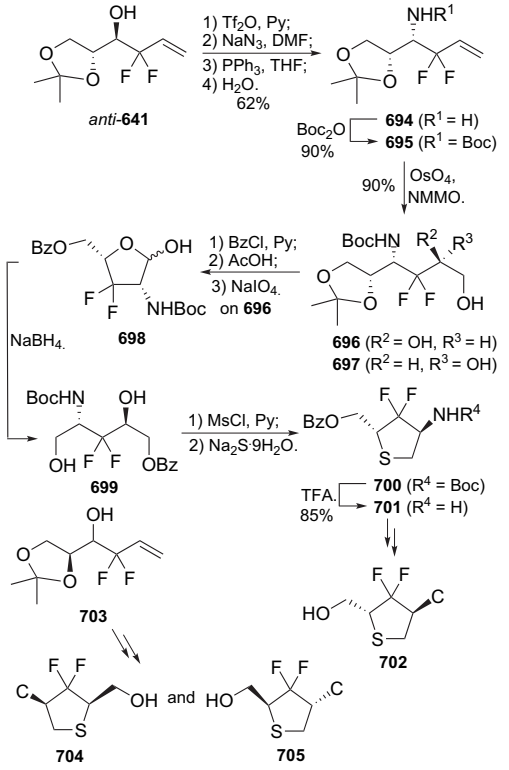
Scheme 108.

Recently, the *gem*-difluorinated alcohol **642** and 3-deoxy-3,3-difluoro-D-*arabino*-furanose **644** were also used to synthesize the *gem*-difluoromethylated thionucleosides **687** and **693** in Qing's group (Scheme 109).[280,289] Access to the nucleoside **687** commenced with the ring opening of the compound **644** with $NaBH_4$/MeOH, and the diol **684** was afforded in quantitative yield. Mesylation of **684** followed by treatment with Na_2S/DMF provided the 4′-thiofuranose **685** in 69% yield. After replacing the Bn group in **685** with a Bz group, the resultant benzoate **686** was subjected to Pummerer glycosylation and further deprotection to give the nucleoside **687** and its C-1′ isomer, which featured both hydroxymethyl and base located in the C-1′ position. On the other hand, the synthesis of the nucleosides **693** highlighted the installation of the AcS group into the compound **688**, the benzoylated derivative of the *gem*-difluorinated alcohol **642**. The thioacetate **689** was furnished in 87% yield and in two steps. Construction of the 3-deoxy-3,3-difluorothiofuranose skeleton was achieved through treatment of the compound **689** with TFA followed by $NaIO_4$-mediated oxidation and acidic methanol hydrolysis. Acetylation of the resultant thiofuranose **690** and subsequent substitution of a Bz group for the Bn group in **691** provided the key intermediate **692**, which was glycosylated with various silylated bases and further deblocked to give the desired nucleosides **693**.

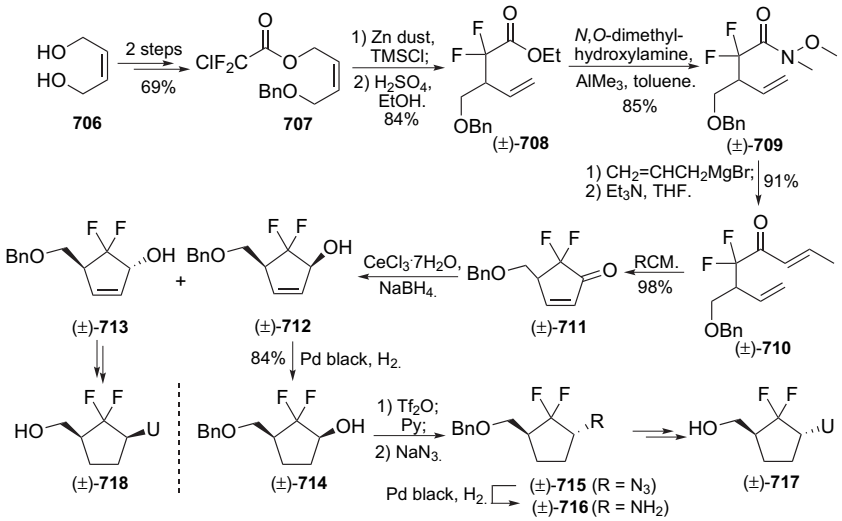


Scheme 109.

Starting from the intermediate *anti*-**641** (Scheme 103), Qing's group also completed the synthesis of 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleoside **702** (Scheme 110), an analogue of 3TC that has



Scheme 110.

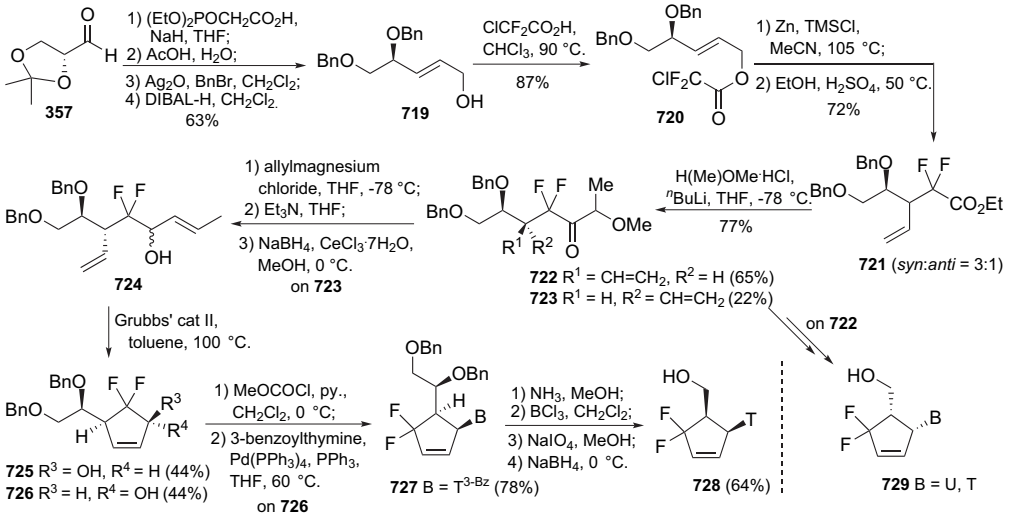


Scheme 111.

high biological activities against HIV and HBV.[290] Their synthesis began with the installation of an amino group into the C-3 position of the compound *anti*-**641**, and the amine **694** was furnished in 62% overall yield. After protection of **694** with Boc, the resultant amide **695** was dihydroxylated to afford the separable diols **696** and **697** in 90% yield and in a 1:1 ratio. Selective benzoylation of the isomer **696** followed by acidic hydrolysis and $NaIO_4$-mediated oxidation gave the difluoromethylated furanose **698**, which was further reduced with $NaBH_4$ to generate the diol **699**. Mesylation of **699** followed by treatment with Na_2S/DMF provided the 4′-thiofuranose **700**, the Boc group of which was removed with TFA to yield the key intermediate **701** in 85% yield. Installation of a pyrimidine base from the amino group of **701** gave the target nucleoside **702** by means of standard methodology. In addition, using a similar strategy, this group recently also accomplished the synthesis of the other 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleosides **704** and **705**, starting from the *gem*-difluorohomoallyl alcohol **703**.[291]

Additionally, in Qing's group, the synthesis of the racemic 2′,3′-dideoxy-6′,6′-difluorocarbocyclic nucleosides (±)-**717** and (±)-**718** highlighted the construction of the carbocyclic ring via ring-closing metathesis (RCM) and the introduction of a CF_2 group by means of a silicon-induced Reformatskii–Claisen reaction of the chlorodifluoroacetic ester **707**, itself available from the 2-butene-1,4-diol **706** in two steps (Scheme 111).[292] The silicon-induced Reformatskii–Claisen reaction of **707** and the following esterification of the resultant acid gave the α,α-difluoroester (±)-**708** in 84% yield, which was further transformed into the Weinreb amide (±)-**709** in 85% yield. After treatment of the amide (±)-**709** with CH_2=$CHCH_2MgBr$ and subsequent double-bond isomerization with Et_3N, the resultant diene (±)-**710** was subjected to RCM reaction to afford the ketone (±)-**711** in 98% yield. Luche reduction of the compound (±)-**711** provided the separable alcohols (±)-**712** and (±)-**713** in a 2.9:1 cis/trans ratio. After hydrogenation of (±)-**712** with Pd black, treatment of the resultant product (±)-**714** with Tf_2O/pyridine followed by a substitution reaction with NaN_3 and further reduction of (±)-**715** gave the cyclic amine (±)-**716**. Installation of uracil base from the amine group of (±)-**716** and removal of the Bn group gave the desired *gem*-difluoromethylated carbocyclic nucleoside (±)-**717**. Using the same reaction conditions, the isomeric nucleoside (±)-**718** was also prepared from (±)-**713**.

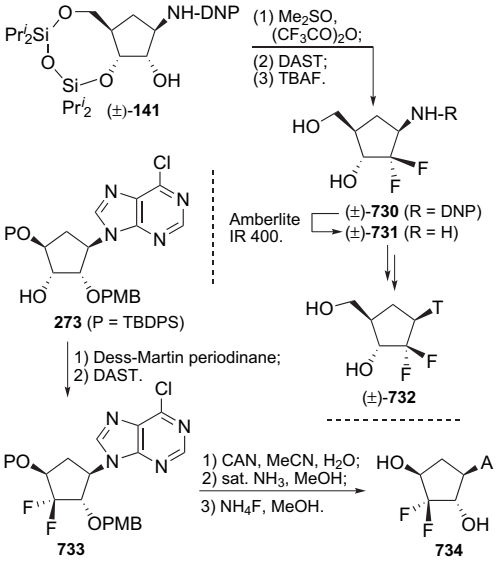
With a stereoselective Reformastskii-Claisen rearrangement, ring-closing methathesis (RCM) and palladium-catalyzed allylic alkylation as the key steps, Qing and co-workers successfully accomplished the synthesis of 3′,3′-difluoro-2′-hydroxymethyl-4′,5′-unsaturated carbocyclic nucleosides from the ester **720** (Scheme 112).[293] Compound **720** was prepared from 1-(*R*)-glyceraldehyde acetonide **357** in five



Scheme 112.

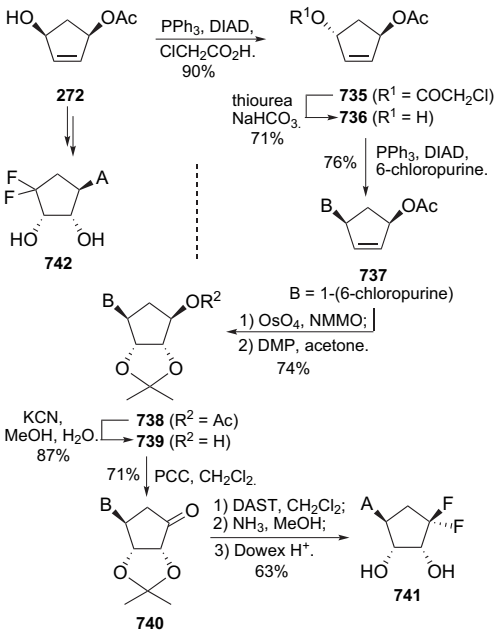
steps, of which the main procedures were Wadsworth–Emmons condensation and esterification of alcohol **719** with $ClCF_2CO_2H$. Silicon-induced Reformastskii-Claisen reaction of **720** and subsequent esterification gave the *gem*-difluorinated ester **721** (*syn*/*anti*=3:1) in 72% yield. Once the ester **721** was converted into the separable Weinreb amides **722** and **723**, preparation of the RCM precursor **724** was completed via treatment with allylmagnesium chloride followed by Luche reduction. Subjecting the alcohol **724** to RCM reaction gave the separable cyclic alcohol **725** and **726** in good yield. Exposure of the intermediate **726** to MeOCOCl/pyridine produced the corresponding allylic carbonate, which reacted with 3-benzoylthymine under the catalysis of $Pd(PPh_3)_4$ to yield the γ-substituted compound **727**. Access to the target nucleoside **728** from **727** was finalized via convenient removal of the benzoyl group and benzyl group, oxidation with $NaIO_4$ and subsequent reduction with $NaBH_4$. Starting from the isomer **722** and using identical procedures, the nucleoside analogues **729** were also prepared in this group.

The synthesis of the racemic *gem*-difluoromethylated carbocyclic nucleoside (±)-**732** was described by Borthwick's group (Scheme 113).[111,112] Their synthesis started from the intermediate (±)-**141** and the key steps involved the Swern oxidation of alcohol (±)-**141** and the subsequent *gem*-difluoromethylation with DAST. After desilylation with TBAF and removal of the DNP protecting group with Amberlite IR 400 (OH^-), thymine base was installed via treatment of the compound (±)-**731** with EtOCH=C(Me)CONCO/DBU followed by hydrochloric acid. In addition, starting from the intermediate **273**, Schneller and co-workers recently developed an entry to the 3′,3′-difluoro carbocyclic nucleoside analogue **734**, just by using a similar method to introduce the *gem*-difluoromethyl group, i.e., oxidation of the secondary hydroxyl group in **273** followed by fluorination with DAST to give key intermediate **733**.[167]



Scheme 113.

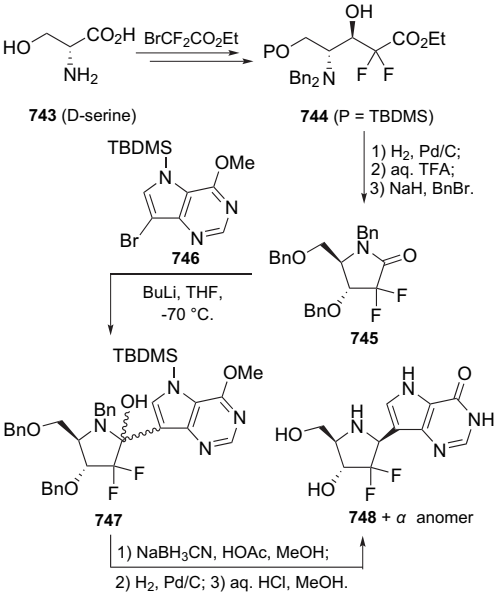
In view of the fact that 5′-noraristeromycin displayed a significant biological activity, due to its apparent inhibition of AdoHcy hydrolase, Schneller and co-workers pursued the synthesis of the 4′,4′-difluoro analogues **741** and **742** of 5′-noraristeromycin (Scheme 114).[294] Their synthesis commenced with treatment of the acetate **272** with $ClCH_2CO_2H$ under Mitsunobu conditions, and the chloroacetate ester **735** was provided in 90% yield. After selective cleavage of the chloroacetate ester moiety in **735** with thiourea/$NaHCO_3$, the resultant hydroxyester **736** was subjected to a second Mitsunobu reaction with 6-chloropurine to give the acetate **737** in 76% yield. Dihydroxylation of the compound **737** and the



Scheme 114.

subsequent isopropylidination afforded the intermediate **738**, which, after deacetylation with KCN/MeCN/H_2O to form **739**, was further oxidized with PCC to furnish the ketone **740**. DAST-mediated *gem*-difluoromethylation of **740** followed by ammonolysis and deisopropylidination provided the desired 4′,4′-difluoro nucleoside analogue **741**. In addition, the enantiomer **742** was also synthesized from the acetate **272**, just by using the same conditions as described for preparing **741** from the hydroxyester **736**.

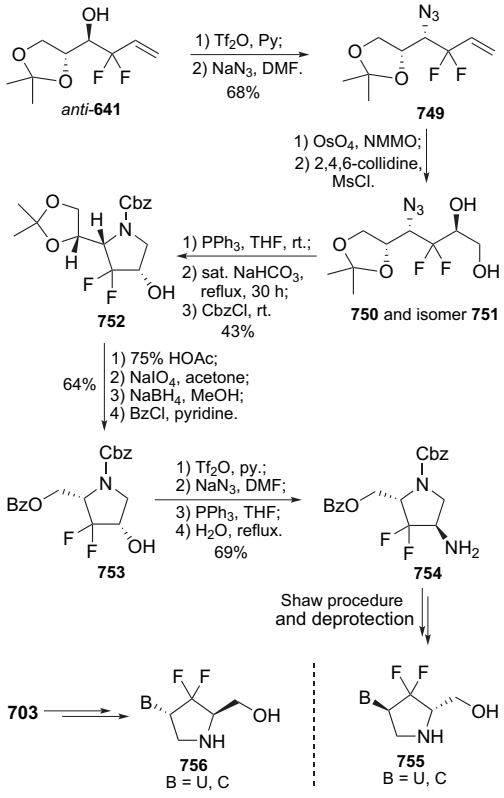
In 2003, Tyler et al. first reported the synthesis and bioactivity of the *gem*-difluoromethylated azanucleosides, 2′-deoxy-2′,2′-difluoro-immucillin-H **748** and its α anomer.[295] With D-serine **743** as the chiral pool and $BrCF_2CO_2Et$ as the *gem*-difluoromethyl source, the lactam **745** was afforded in a straightforward fashion via **744** (Scheme 115). Lithiation of the 9-bromo-9-deazahypoxanthine derivative **746** by bromine–-lithium exchange and subsequent addition of the lactam **745** to the reaction mixture provided the



Scheme 115.

alcohol **747**, the reduction of which with $NaBH_3CN$ followed by hydrogenolysis and acidic hydrolysis delivered the nucleoside **748** and its α anomer.

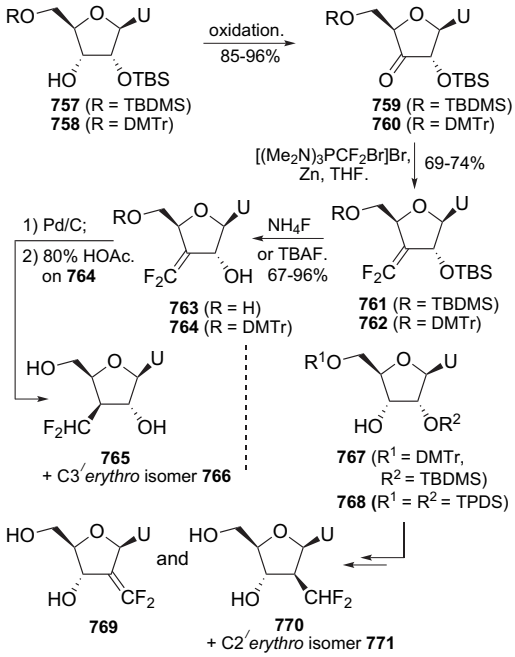
Very recently, several 2′,3′-dideoxy-6′,6′-difluoro-3′-azanucleosides were synthesized in Qing's group. The synthesis featured an efficient construction of the fluorine-containing pyrrolidine ring (Scheme 116).[296] Starting from the intermediate *anti*-**641**, the azide derivative **749** was provided via trifluoromethylsulfonation followed by treatment with NaN_3. Subjecting **749** to dihydroxylation and subsequent monomesylation gave the diol **750** and its isomer **751**. The pyrrolidine ring intermediate **752** was delivered by the reduction of **750** using PPh_3 followed by in situ protection with CbzCl. Conversion of the isopropylidene ketal moiety into a hydroxymethyl group was realized in three steps, including acid hydrolysis, oxidative scission of the resultant diol and reduction. Transformation of the hydroxyl group in **753** into an amine group was fulfilled in traditional steps, including trifluoromethylsulfonation, azidation and PPh_3-mediated reduction. Finally, the desired *gem*-difluorinated azanucleosides **755** were accessed from the amine **754** by installing the pyrimidine bases based on the procedure of Shaw and Warrener.[111] Starting from the *gem*-difluorohomoallyl alcohol **703** and using a similar synthetic route, 2′,3′-dideoxy-6′,6′-difluoro-3′-azanucleosides **756** were also prepared.



Scheme 116.

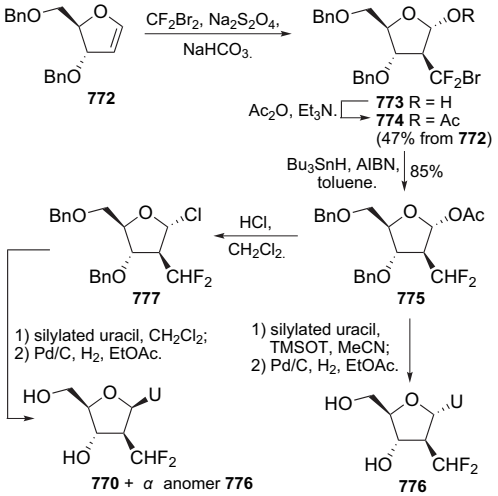
3.3. Difluoromethylated or difluoromethylenated nucleosides

After Walker's group, in 1990, accomplished the synthesis of 3′-difluoromethylated nucleosides by means of reactions of the protected 3′-*C*-formyl nucleosides with DAST,[70] Serafinowski and co-workers described the synthesis of the 3′-difluoromethylenated nucleoside **763** and the 3′-difluoromethylated nucleoside **765**, starting from the protected uridines **757** and **758**.[297–299] Their synthesis commenced with the oxidation of the compounds **757** and **758** to the ketones **759** and **760**, which were treated with $[(Me_2N)_3PCF_2Br]Br/Zn$ to give the 2′-difluoromethylenated derivatives **761** and **762**, respectively (Scheme 117). Removal of the silyl groups in the compounds **761** and **762** provided the 2′-difluoromethylenated nucleoside **763** and the protected nucleoside **764**, respectively. Hydrogenation of the compound **764** followed by detritylation delivered the desired 2′-difluoromethylated nucleoside **765** and its C3′ *erythro* isomer **766**. In addition, this group also fulfilled the synthesis of the 2′-difluoromethylenated nucleoside **769** and the 2′-difluoromethylated nucleoside **770** from the suitably protected uridines **767** and **768** using similar reaction conditions.



Scheme 117.

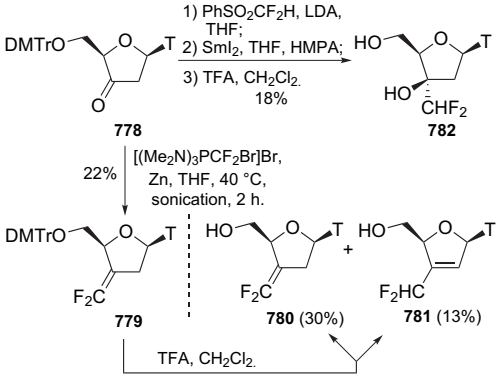
Interestingly, Quirion's group developed a novel synthetic route to 2′-deoxy-2′-difluoromethyluridine **770** and its α anomer **776** in 2001.[300] Quirion's route featured the addition of CF_2Br_2 to the protected glycal **772** to stereoselectively give the α-2′-deoxy-2′-bromodifluoromethylarabinose **773** (Scheme 118). After acetylation of compound **773**, the resultant compound **774** was subjected to a radical reductive process (Bu_3SnH/AIBN) to afford the acetate **775**



Scheme 118.

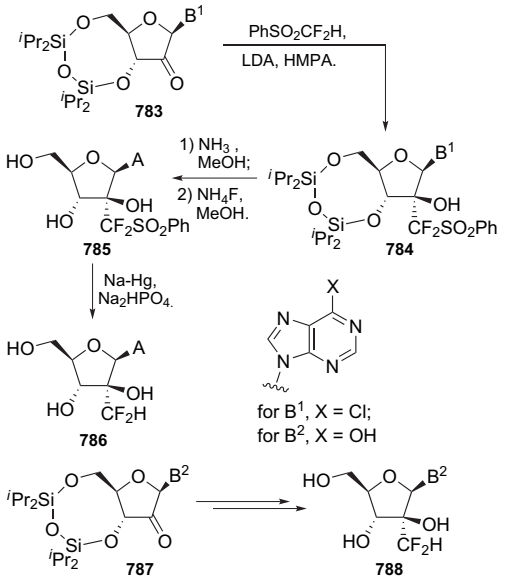
in 85% yield. The desired nucleosides **776** and **770** were obtained from the intermediate **775** using two different procedures, one of which was glycosylation of **775** with silylated uracil, and the other involved coupling of the α-chlorodeoxyarabinose **777** with silylated uracil.

Using an ultrasound-assisted reaction between the 3′-oxo derivative **778** of thymidine and $[(Me_2N)_3PCF_2Br]Br/Zn$ as the key step, Serafinowski and co-worker also realized the synthesis of 3′-difluoromethylene-3′-deoxythymidine **780** and other related derivatives (Scheme 119).[301] In their synthesis, exposure of the compound **778** to $[(Me_2N)_3PCF_2Br]Br$(8 equiv)/Zn in a sonic bath at 40 °C gave the desired 3′-difluoromethylene derivative **779** in 22% yield, which was further treated with 2% TFA in CH_2Cl_2 to afford the 3′-difluoromethylene-3′-deoxythymidine **780** and its tautomerised compound **781**. In addition, this group also completed the synthesis of 1-(3-difluoromethyl-β-D-*threo*-pentofuranosyl)thymine **782** in 18% overall yield through the addition of difluoromethyl phenyl sulfone to the compound **778** followed by reductive desulfonylation with SmI_2 and removal of the DMTr protecting group with TFA.



Scheme 119.

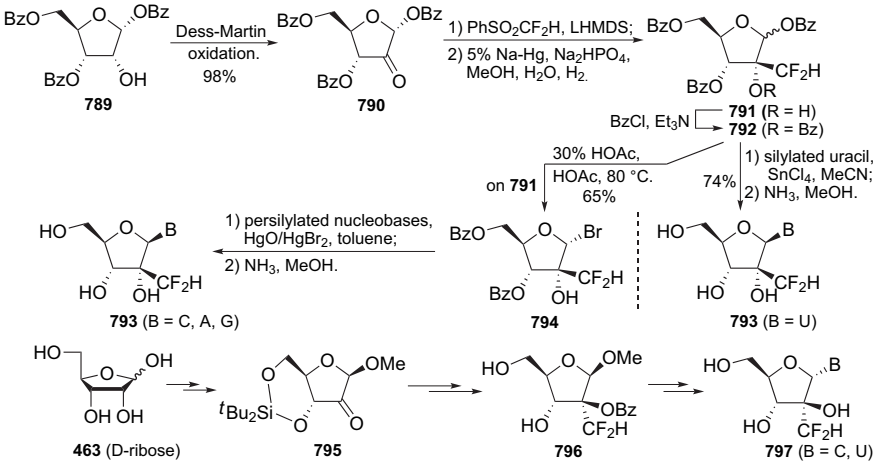
The synthesis of the 2′-*C*-difluoromethyl adenosine **786** was accomplished through alkylation of the ketone **783** with phenyl difluoromethyl sulfone/LDA (Scheme 120).[302] Ammonolysis of the product **784** and subsequent desilylation with NH_4F/MeOH gave the adenosine analogue **785**, which was further subjected to Na/Hg/Na_2HPO_4-mediated desulfonylation to provide the desired nucleoside **786**. It should be pointed out that, starting from the ketone **787**, the inosine analogue **788** was also synthesized by the same group using a similar synthetic route.



Scheme 120.

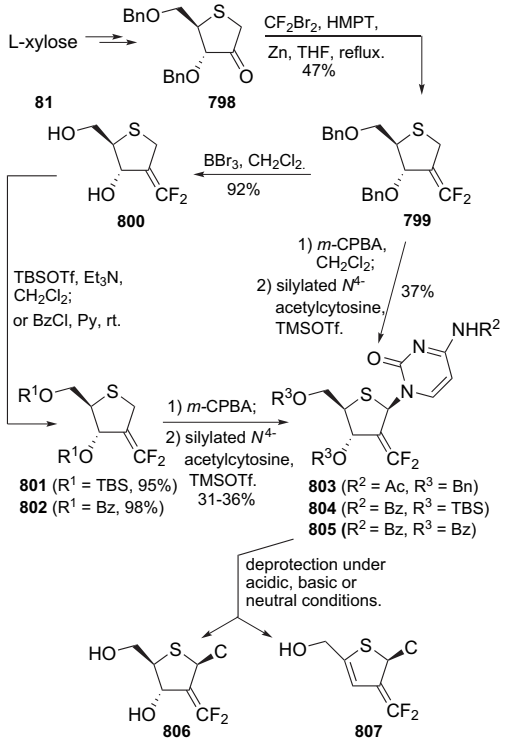
Recently, Piccirilli's group described a synthetic entry to 2′-C-β-difluoromethylribonucleosides **793**.[303] Their method commenced with the construction of the glycosylating agent **792** in several steps from 1,3,5-tri-*O*-benzoyl-α-D-*ribo*-furanose **789,** and the key steps included the nucleophilic addition of $PhSO_2CF_2H$ to the ketone **790** followed by mild and efficient reductive desulfonation (Scheme 121). Glycosylation of the compound **792** with bis(trimethylsilyl)uracil and subsequent debenzoylation gave the difluoromethyluridine **793** (B=U). Conversion of the compound **791** into the corresponding *ribo*-furanosyl bromide **794** allowed the access to the C, A and G analogues, which were obtained through coupling of the bromide **794** with persilylated nucleobases in the presence of $HgO/HgBr_2$. In addition, using a similar method to introduce a difluoromethyl group into the C-2′ position of the intermediate **795**, this group also developed a related approach to synthesize 2′-*C*-α-difluoromethyl-*arabino*-α-pyrimidine **797**, starting from D-ribose **463** and proceeding via **796**.

Designed as a potential antitumour agent, 2′-deoxy-2′-*C*-difluoromethylene-4′-thiocytidine **806** was synthesized by Jeong and co-workers, starting from L-xylose **81** (Scheme 122).[304] After the ketone **798** was prepared from L-xylose in several steps, treatment of the intermediate **798** with CF_2Br_2/HMPT/Zn under refluxing THF afforded the difluoromethylenated derivative **799** in 47% yield. Removal of the benzyl groups in **799** with BBr_3 furnished the



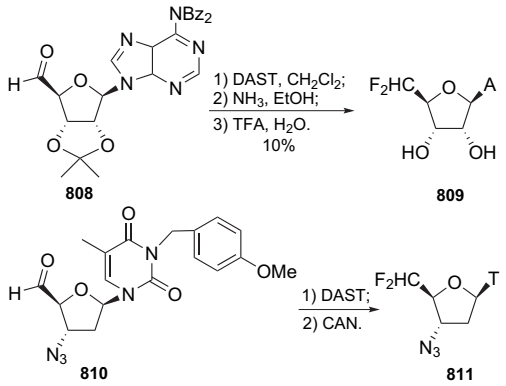
Scheme 121.

diol **800** in high yield, which was disilylated or dibenzoylated to produce the the disilylated compound **801** or the dibenzoate **802**. After oxidation of **799**, **801** and **802** with *m*-CPBA, the resultant sulfoxides were condensed with silylated cytosine to give the protected nucleosides **803**, **804** and **805**, respectively. Interestingly, Jeong et al. found that removal of the protecting groups in the compounds **803**–**805** under acidic or basic conditions always delivered the elimination product **807** as the major product. Using neutral reaction conditions, however, instead of acidic or basic conditions exclusively afforded the desired nucleoside **806**.



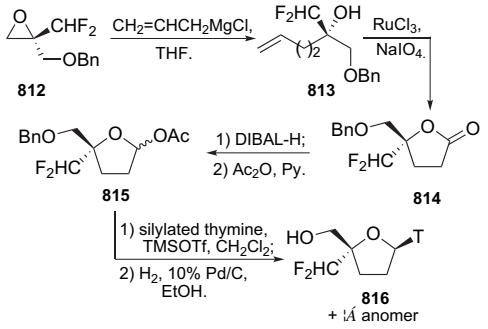
Scheme 122.

In 1991, McCarthy and co-workers completed the synthesis of 5′-deoxy-5′-difluoromethyladenosine **809**, through the DAST-mediated fluorination of N^6,N^6-dibenzoyl-2′,3′-*O*-isopropylideneadenosine 5′-aldehyde **808**, followed by removal of the isopropylidene ketal and Bz protecting groups (Scheme 123).[305] In addition, synthesis of the 3′-azido-3′,5′-dideoxy-5′,5′-difluorothymidine **811** was also accomplished from the intermediate **810**, using a similar strategy, in Coe's group.[306]



Scheme 123.

Bravo et al. described the synthesis of 4′-difluoromethyl-3′-deoxythymidine **816** and its α anomer, starting from the α-difluoromethylated cyclopropane intermediate **812** (Scheme 124).[307] As the important step of their synthesis, exposure of the compound **812** to allylmagnesium chloride in THF yielded the alcohol **813**, which was oxidized with $NaIO_4/RuCl_3$ to afford the lactone **814**. Reduction of **814** with DIBAL-H and subsequent acetylation of the resultant lactol provided the intermediate **815**. Glycosylation of **815** with silylated thymine followed by removal of the benzyl group via hydrogenation gave the desired nucleoside **816** and its α anomer.

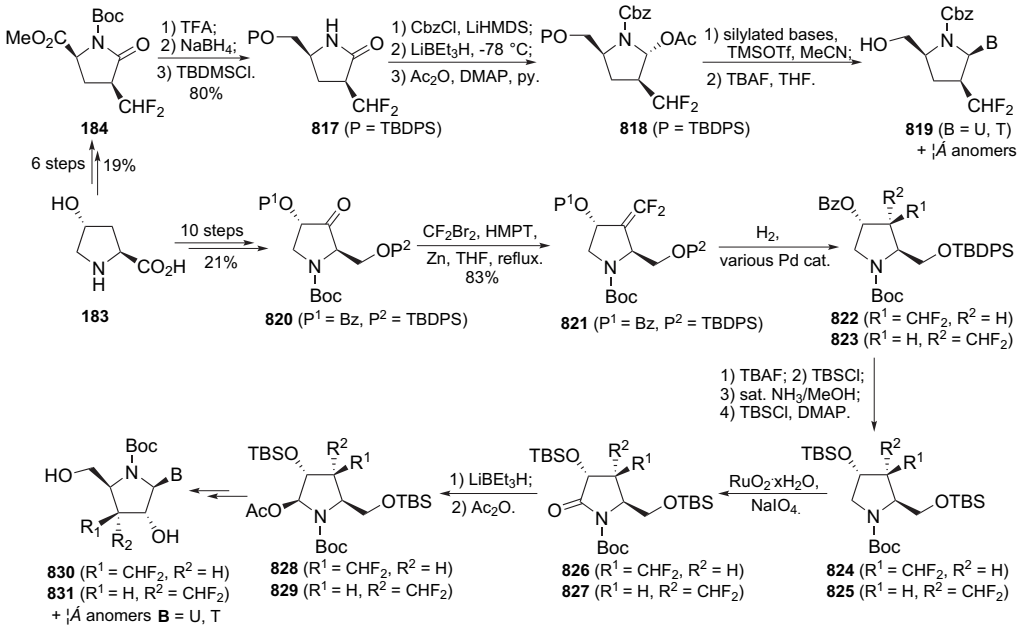


Scheme 124.

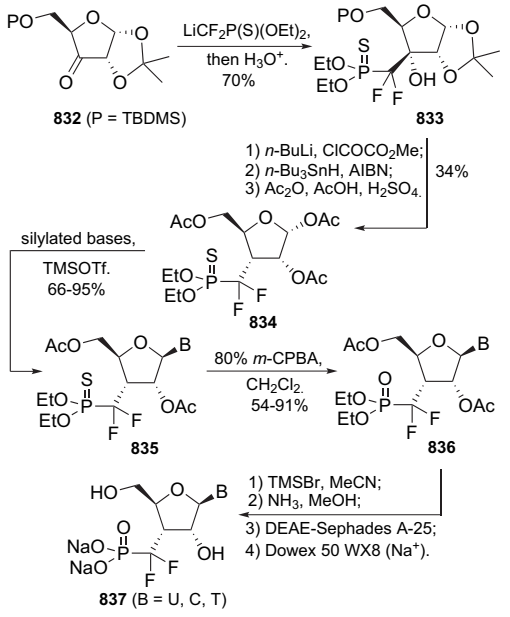
Qing and Qiu carried out the synthesis of the 2′,3′-dideoxy-3′-difluoromethyl azanucleosides **819**[126] and 3′-deoxy-3′-difluoromethyl azanucleosides **830** and **831**,[308] starting from the same natural amino acid **183** (Scheme 125). After preparing the amide **184** from **183** in 19% yield over six steps**,** removal of the Boc group with TFA followed by reduction of the ester with $NaBH_4$ and silylation of the generated hydroxyl group gave the amide **817** in 80% overall yield, which was further converted into the acetate **818** in three steps. Coupling of **818** with silylated bases and desilylation with TBAF gave the desired azanucleosides **819** and the corresponding α anomers. The synthesis of the azanucleosides **830** and **831** commenced with the conversion of the amino acid **183** into the ketone **820** in 21% yield over 10 steps. Difluoromethylenation of compound **820** gave the terminal *gem*-difluoromethylenated alkene **821** in 83% yield, which was further subjected to hydrogenation to furnish two separable diastereoisomers **822** and **823**. After replacing all the hydroxy protecting groups with TBS, the resultant products **824** and **825** were oxidized with $RuO_2\times H_2O$/$NaIO_4$ to yield the amides **826** and **827**, respectively. Reduction of **826** and **827** with $LiBEt_3H$ followed by acetylation with Ac_2O/Et_3N provided the precursor compounds **828** and **829**, respectively, from which the desired nucleosides **830** and **831** were obtained through glycosylation with silyated bases and subsequent desilylation.

3.4. Phosphonodifluoromethylenated nucleosides

Fluorinated phosphonates play important roles as antiviral agents, biomedical agents, potential enzyme inhibitors and useful probes for the elucidation of biochemical processes.[309] Based on both electronic and steric considerations, it has been suggested that α,α-difluoromethylphosphonates should mimic phosphate esters better than the corresponding phosphonates. The first and efficient synthesis of phosphonodifluoromethylene analogues **837** of nucleoside 3′-phosphates was reported by Piettre and co-workers.[310] The key steps of their synthetic strategy involved the stereoselective addition of the lithium salt of difluoromethylphosphonothioate to the readily available ketone **832** and the conversion of the P═S bond in the phosphonothioates **835** into the P═O bond through oxidation with *m*-CPBA (Scheme 126). After removal of all the



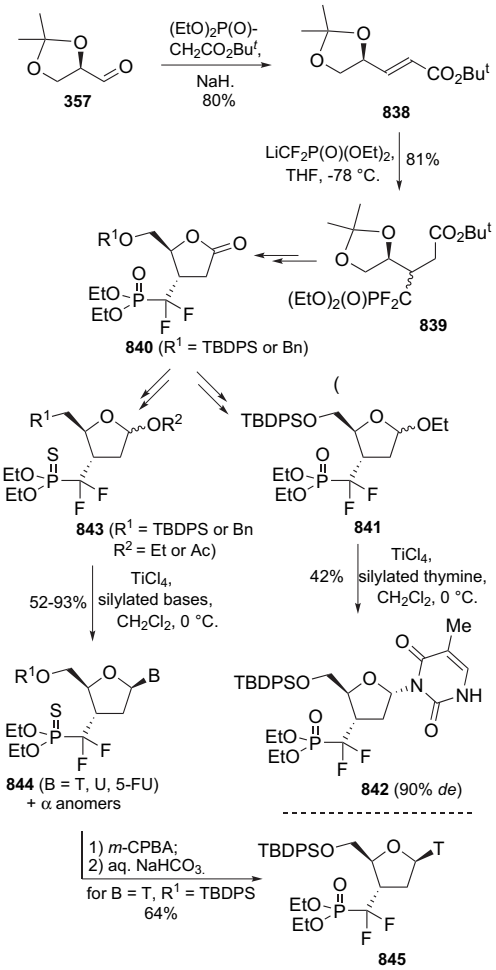
Scheme 125.



Scheme 126.

protecting groups, the desired nucleoside 3′-phosphate analogues **837** were provided in the form of their disodium salts. It is of interest to note that the synthetic strategy was improved by using the organomagnesium reagent $BrMgCF_2P(S)(OEt)_2$ instead of $LiCF_2P(S)(OEt)_2$ and using 4-chlorobenzoyl instead of TBDMS as the protecting group.[311]

Yokomatsu's group carried out an in-depth investigation into the $TiCl_4$-mediated N-glycosylation of 2′,3′-dideoxyfuranose derivatives bearing difluoromethylene-phosphonate and -phosphonothioate functional groups at the 3α-position and synthesized a series of (diethoxyphosphorothioyl)difluoromethyl and (diethoxyphosphonyl)difluoromethyl-containing nucleotide analogues.[312,313] After the key intermediates, the 1-ethoxy derivative **841** and the phosphonothioate analogues **843**, were prepared, starting from the (*R*)-glyceraldehyde derivative **357** (Scheme 127), they found that N-glycosylation of **841** with

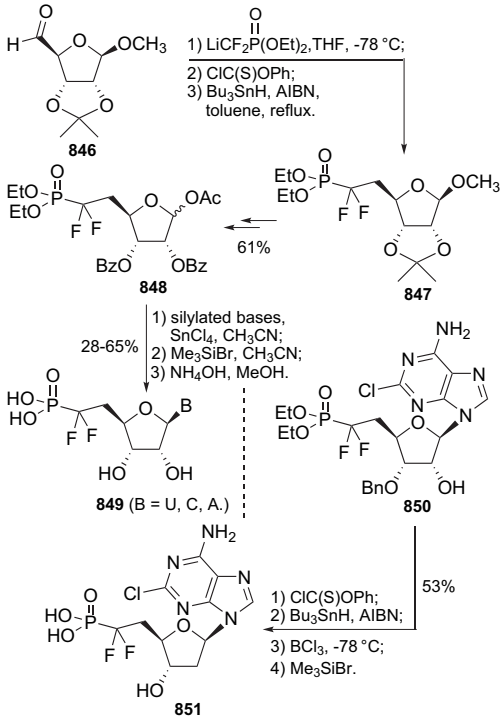


Scheme 127.

silylated thymine at 0 °C in CH_2Cl_2 in the presence of $TiCl_4$ gave the α-N^3-nucleotide analogues **842** in high diastereomeric excess (90% de) and in 42% yield. N-glycosylation of **843** with silylated

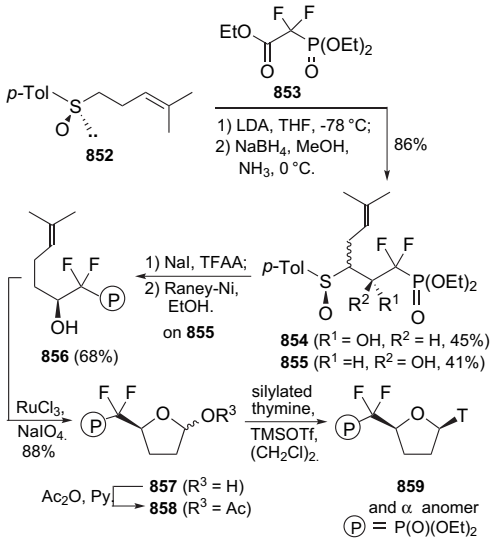
bases, however, provided the N^1-nucleotide analogues in 52–93% yield with the β anomers as the main products. In addition, this group also found that the reactivities with respect to $TiCl_4$-mediated N-glycosylation of the compound **843** were significantly affected by the reaction temperature, i.e., a high reaction temperature benefitted the formation of the N^1-adduct and a low reaction temperature availed the formation of the N^3-adduct. The nucleotide analogue **844** (B=T, R^1=TBDPS) was converted into the difluoromethylenephosphonate analogue **845** in 64% yield by oxidation with *m*-CPBA. Different Lewis acid-mediated N-glycosylation of 2,3-dideoxy-*ribo*-funanoside **843** (R^1=TBDPS, R^2=Et) with silylated N^6-benzoyladenine nucleobases was also studied in detail by this group.[313]

The synthesis of nucleoside 5′-deoxy-5′-difluoromethylphosphonates **849** was reported by Usman and co-workers.[314,315] Their synthesis commenced with the conversion of the 5-aldehyde **846** into the D-ribose α,α-difluoromethylphosphonate **847** through treatment with $LiCF_2P(O)(OEt)_2$ followed by radical deoxygenation (Scheme 128). After transformation of the protecting groups in **847**, Vorbrüggen glycosylation of the resultant acetate **848** with various silylated bases followed by *de*-esterification with Me_3SiBr/MeCN and *de*benzoylation with NH_3/MeOH gave the free 5′,6′-dideoxy-6′-(dihydroxyphosphinyl)-6′,6′-difluoro nucleoside analogues **849**. The compound, 2-chloro-2′,5′-dideoxy-5′-difluoromethylphosphinyladenosine **851**, was also synthesized using a similar synthetic route, which additionally involved reductive *de*oxygenation of the 2′-hydroxyl in the 3′-protected ribonucleotide analogue **850**.[316]



Scheme 128.

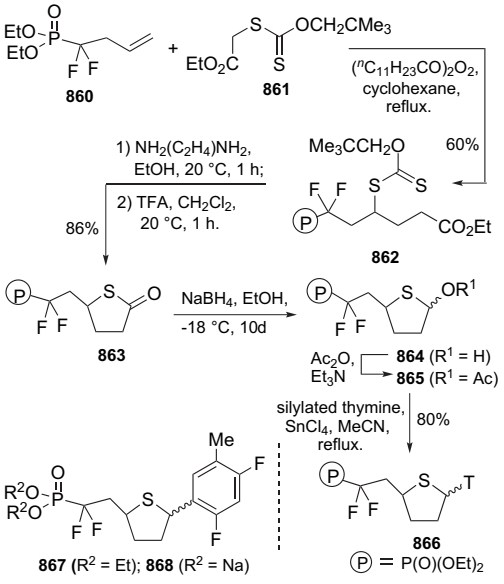
Starting from 2-methyl-5-(4-methylphenylsulfinyl)pent-2-ene **852** and ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate **853**, 2′,3′,5′-trideoxy-4′-[(diethoxyphosphoryl)difluoromethyl]thymine analogues **859** were synthesized by Bravo and co-workers.[317] Their synthesis was carried out by making the intermediate **855** in 41% yield. Subsequent deoxygenation with NaI/TFAA and hydrogenolytic cleavage of the sulfinylic carbon–sulfur bond with Raney-Ni gave the alcohol **856** in 68% yield (Scheme 129). Oxidative cleavage of **856** generated the lactol **857** in 88% yield, which was acetylated to provide the acetyl derivative **858**. Coupling of **858** with



Scheme 129.

persilylated thymine gave the desired 4′-[(diethoxyphosphoryl)difluoromethyl]nucleoside analogue **859** and its α anomer.

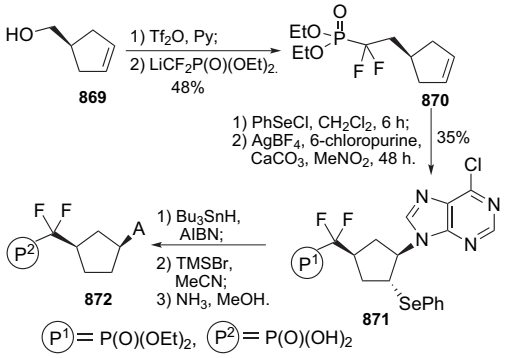
Zard's group, in 1998, utilized an expedient radical-based approach to realize the synthesis of the difluorophosphonate analogues of thionucleosides.[318] In their synthesis, the key radical addition took place upon heating the olefin **860** and the xanthate **861** with lauroyl peroxide as the initiator, and the xanthate **862** was afforded in 60% yield (Scheme 130). Cleavage of the xanthate group via exposure of **862** to an excess of $NH_2(C_2H_4)NH_2$/EtOH followed by treatment with TFA gave the thiolactone **863** in 86% yield. After reduction of **863** and subsequent acetylation, the resultant intermediate **865** was subjected to Vorbrüggen coupling with silylated thymine to provide the target thionucleoside analogue **866** in good yield. Additionally, this group also fulfilled the synthesis of the thionucleosides **867** and **868** bearing an aromatic ring using a similar radical-addition reaction.



Scheme 130.

An entry into the carbocyclic difluorophosphonate analogue **872** of dideoxypurine nucleotide was developed by Halazy and Wolff-Kugel.[319] Their synthesis highlighted the 'purino-selenenylation' of

the difluoromethylenephosphonate **870**, itself available through condensing the triflate of the alcohol **869** with $LiCF_2P(O)(OEt)_2$ (Scheme 131). After reaction of the compound **870** with PhSeCl in CH_2Cl_2 for 6 h, the yielded seleniranium salt was further treated with $AgBF_4$/6-chloropurine/$CaCO_3$ in $MeNO_2$ to afford the adduct **871** in 35% yield. Conversion of **871** into the target nucleotide **872** was accomplished in a straightforward fashion via cleavage of the carbon–selenium bond with Bu_3SnH/AIBN, removal of the ethyl protecting group with TMSBr and subsequent ammonolysis in MeOH at 100 °C in a steel cylinder.



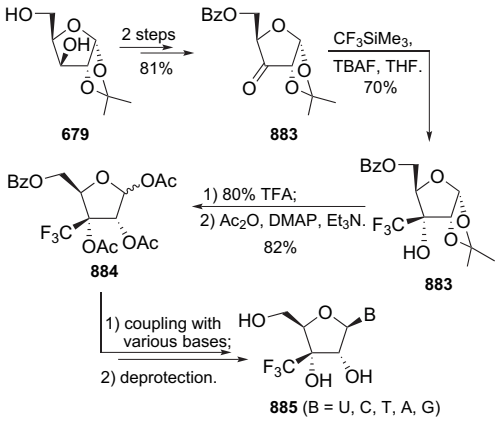
Scheme 131.

4. Trifluoromethylated nucleosides

Many advantages could be expected from the presence of a CF_3 group on the sugar moiety of nucleosides, including increasing lipophilicity[320] and improved chemical and/or enzymatic stability.[321,322] In addition, the trifluoromethyl group can enhance the therapeutic properties of bioactive compounds.[323–325] It should also be noted that Bansal has proposed that replacement of the methyl group in the fucose residue with the more hydrophobic trifluoromethyl group might provide an artificial inhibitor for Le^x–Le^x interaction.[326] Taking all of the above considerations into account and in order to discover new nucleoside derivatives with high antiviral activities, the introduction of a trifluoromethyl group into nucleosides has recently attracted more and more attention.

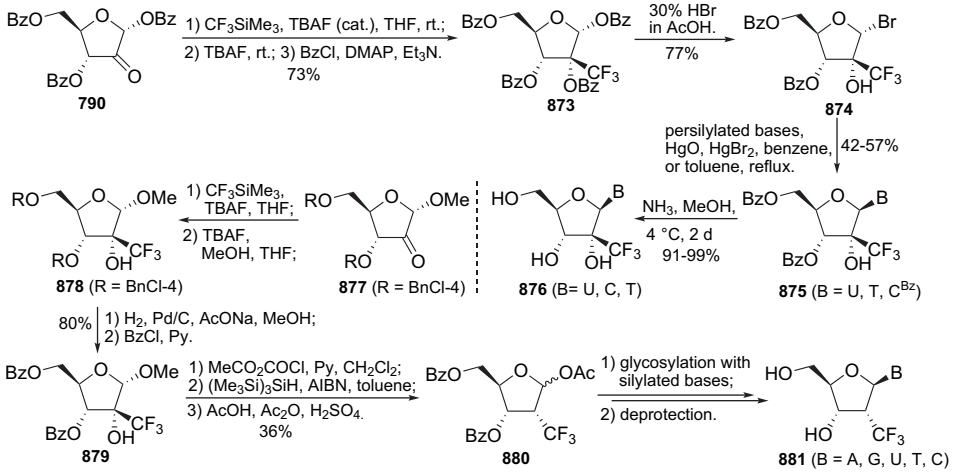
The first synthesis of 2′-*C*-β-trifluoromethyl pyrimidine ribonucleosides **876** was reported by Piccirilli's group.[327] After the intermediate **873** was prepared through treatment of the ketone **790** with a Ruppert–Prakash reagent (CF_3SiMe_3) followed by desilylation and benzoylation (Scheme 132), this group discovered that the Hilbert–Johnson glycosylation of **873** required an unusually high temperature (>120 °C) and a long reaction time. Glycosylation of the 1-bromo derivative **874** with silylated pyrimidines in the presence of HgO/$HgBr_2$ at 80–85 °C, however, exclusively afforded the β anomers **875** in 42–57% yield. Deprotection of the compounds **875** with NH_3/MeOH provided the target nucleosides **876** in high yield. Two years later, Mathé and co-workers accomplished the synthesis of 2′-deoxy-2′-*C*-trifluoromethyl-β-D-ribonucleoside derivatives **881** from the ketone **877**.[328] Interestingly, Mathé et al. found that Hilbert–Johnson glycosylation of the peracylated 2-deoxy-2-*C*-trifluoromethyl sugar **880** with silylated uracil or thymine proceeded well at 50 °C. In their synthesis, the key intermediate **880** was prepared from the ketone **877** in several steps, which included trifluoromethylation of **877** with CF_3SiMe_3, conversion of the protecting groups into Bz groups and deoxygenation of the alcohol **879**.

Pioneered by Johnson's group[329] and followed by the Mathé group,[330] 3′-*C*-trifluoromethyl-β-D-ribonucleoside derivatives **885** were synthesized, starting from 1,2-isopropylidene-D-xylose **679**, which was first converted into the ketone **882** in 81% overall yield (Scheme 133). Trifluoromethylation of **882** with CF_3SiMe_3/TBAF afforded the alcohol **883** in 70% yield. After *de*isopropylidenation with TFA and acetylation with Ac_2O/DMAP, coupling of the resultant triacetate **884** with various nucleic acid bases and subsequent removal of all the protecting groups provided the desired trifluoromethylated nucleosides **885**.

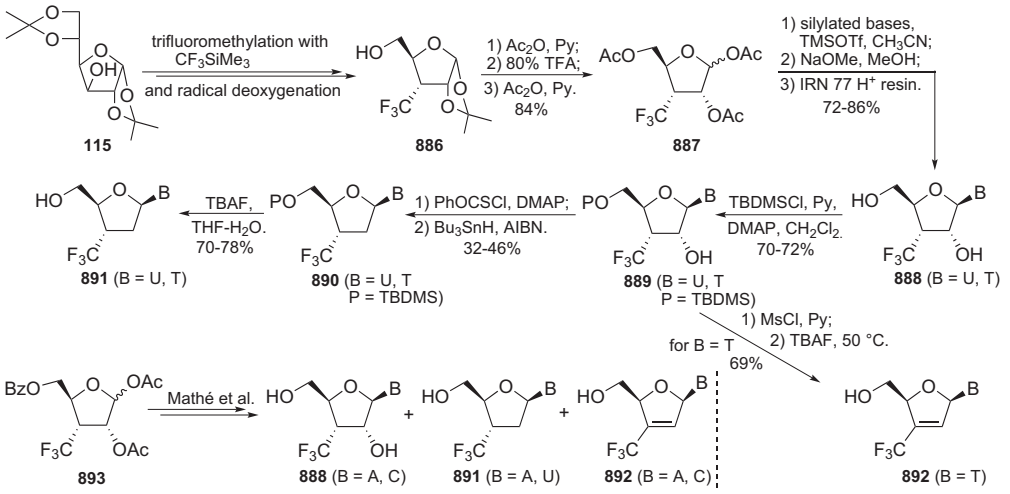


Scheme 133.

In 1998, Portella and co-workers developed an efficient route to the 3′-deoxy-3′-*C*-CF_3 and 2′,3′-dideoxy-3′-*C*-CF_3 and 2′,3′-unsaturated-3′-*C*-CF_3 nucleoside derivatives **888** (B=U, T), **891** (B=U, T) and **892** (B=T) (Scheme 134).[331] Their synthesis commenced with



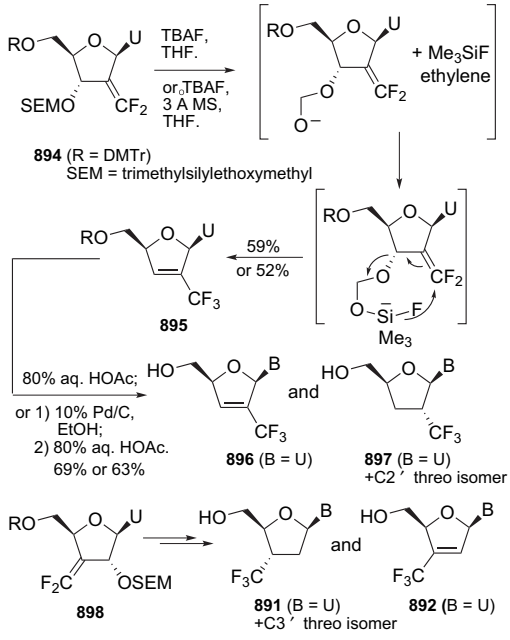
Scheme 132.



Scheme 134.

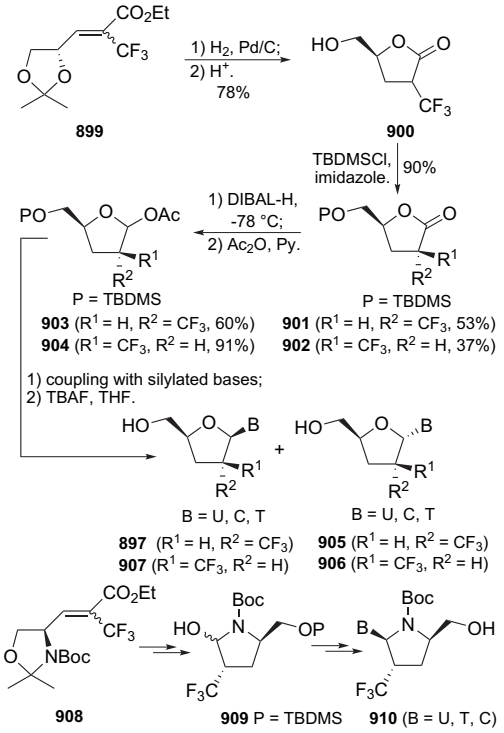
the intermediate **886**, which was prepared from the D-xylose derivative **115** by a reaction sequence where the key steps, trifluoromethylation with CF_3SiMe_3 and radical deoxygenation, are highly stereoselective.[332] After a simple transformation of the functional groups in **886**, subjecting the resultant triacetate **887** to Vorbrüggen glycosylation followed by deacetylation gave the desired nucleosides **888** (B=U, T). Access to the dideoxy derivatives **891** (B=U, C) from the compounds **888** was realized through silylation of the hydroxyl group, radical deoxygenation at C-2 in the alcohols **889** and final deprotection. In addition, the compound **889** (B=T) was also converted into the 2′,3′-unsaturated-3′-*C*-CF_3 nucleoside derivative **892** (B=T) via mesylation followed by TBAF-mediated elimination. It should be noted that, using a similar strategy, Mathé and co-workers also synthesized the corresponding adenosine and cytidine analogues **888** (B=A, C), **891** (B=A, U) and **892** (B=A, U), starting from the benzoylated intermediate **893**.[333,334]

Interestingly, the synthesis of the 2′-trifluoromethyl-2′,3′-dideoxyuridine derivatives **896** and **897** (B=U) was accidentally developed by Serafinowski and Brown in 2000.[335] They found that treatment of the 2′-deoxy-2′-difluoromethylenyl uridine derivative **894** with TBAF in THF in the absence or presence of 3 Å MS gave the 2′,3′-unsaturated-2′-trifluoromethyl uridine derivative **895** in medium yields (59 or 52%) (Scheme 135). The mechanism of this special transformation was proposed to involve an initial attack of F^- at silicon, with the expulsion of trimethylsilyl fluoride and ethylene. Direct removal of the DMTr protecting group in **895** with 80% HOAc, or hydrogenation of **895** followed by removal of the DMTr protecting group, gave the nucleosides **896** and **897** (C2′ *threo* isomer), respectively. Utilizing similar reaction conditions, the 3′-trifluoromethylated nucleosides **891** (B=U) and **892** (B=U) were also synthesized, starting from the 3′-deoxy-3′-difluoromethylenyl uridine derivative **898**.



Scheme 135.

In the same year, Qing's group presented another synthetic route to 2′,3′-dideoxy-2′-trifluoromethyl nucleosides **897** (B=U, T, C), **907** (B=U, T, C) and their anomers **905** and **906** (Scheme 136).[336] Starting from the α-trifluoromethyl-α,β-unsaturated ester **899,** Qing and co-workers first obtained the lactone **900** through hydrogenation and subsequent acidic treatment. Silylation of the



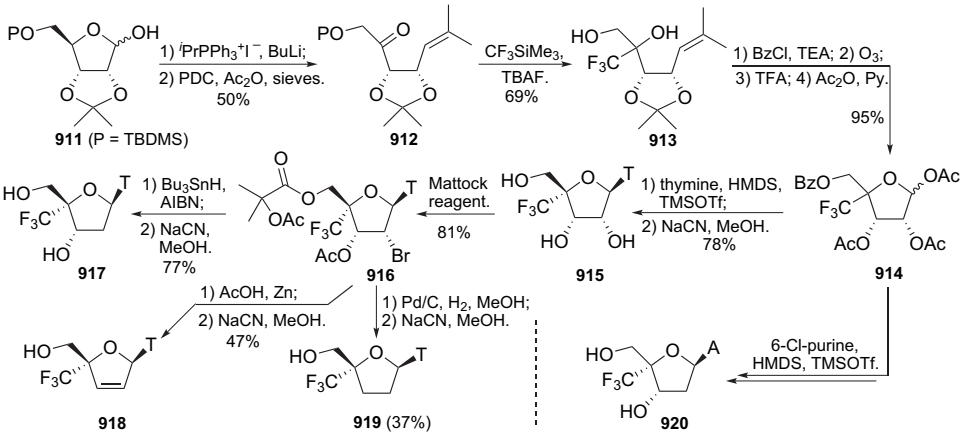
Scheme 136.

alcohol **900** gave the separable lactones **901** and **902**, which were reduced with DIBAL-H followed by acetylation to afford the compounds **903** and **904**, respectively. Coupling of the acetates **903** and **904** with silylated pyrimidines followed by deprotection gave the desired nucleosides **897** (B=U, T, C), **907** (B=U, T, C) and their anomers **905** and **906**, respectively. It should be noted that this group has also carried out the synthesis of L-2′,3′-dideoxy-2′-trifluoromethyl-*N*-azanucleosides **910** from the α-trifluoromethyl-α,β-unsaturated ester **908** using a similar synthetic route.[337]

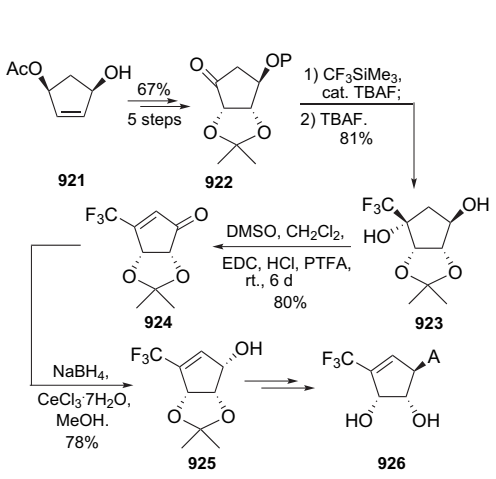
Johnson and Kozak presented an efficient strategy for the introduction of a CF_3 group into the C-4 position of ribose derivatives, and this strategy was successfully utilized in the synthesis of various 4′-trifluoromethylated nucleoside analogues.[338] Their synthesis commenced with the masking of the aldehyde moiety of the D-ribose-derived lactol **911** as an olefin and subsequent oxidation of the generated alcohol (Scheme 137). Then, treatment of the ketone **912** with CF_3SiMe_3/TBAF gave the diol **913** in 69% yield, which was converted into the acetate **914** as a mixture of D-*ribo* and L-*lyxo* isomers through regioselective benzoylation, ozonolytic cleavage, removal of isopropylidene ketal with TFA and peracetylation. Coupling of **914** with silylated thymine followed by separation of the 4′-epimers and removal of all the protecting groups afforded the 4′-CF_3-5-methyluridine **915** in 78% yield. In addition, exposure of the triol **915** to a Mattock reagent (α-acetoxyisobutyryl bromide) gave the bromide **916**, from which the nucleosides 4′-CF_3-thymidine **917**, 4′-CF_3-2′,3′-dideoxy-2′,3′-didehydrothymidine **918** and 4′-CF_3-2′,3′-dideoxy-thymidine **919** were provided through treatment with Bu_3SnH/AIBN followed by deprotection, treatment with Zn/AcOH followed by deprotection, and hydrogenation with Pd/C, H_2, MeOH followed by deprotection, respectively. Johnson and Kozak also completed the synthesis of 4′-CF_3-2′-deoxyadenosine **920** from the intermediate **914**.

Schneller's group, in 2005, described a 12-step enantiospecific synthesis of 5′,5′,5′-trifluoro-5′-deoxyneplanocin A **926**. Their synthesis began with the chiral acetate **921** and its conversion into the ketone **922** through a five-step sequence of reactions (Scheme 138).[339] A CF_3SiMe_3-mediated trifluoromethylation of compound **922** and subsequent desilylation provided the diol **923**, which was further subjected to a modified Pfitzner–Moffatt oxidation to give the enone **924** in 80% yield. A Luche reduction of the enone **924** yielded the alcohol **925**, from which the target nucleoside **926** was furnished through a Mitsunobu reaction with 6-chloropurine followed by ammonolysis and acidic deprotection.

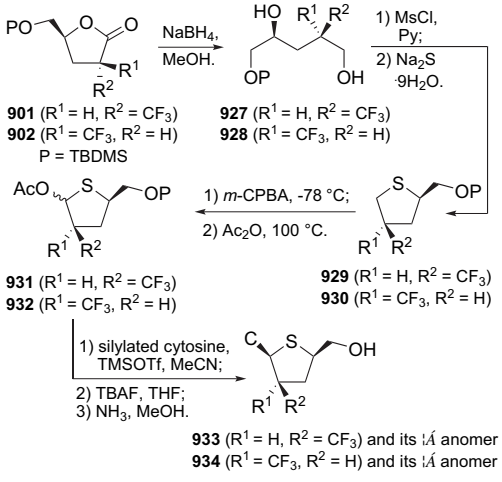
Starting from the lactones **901** and **902**, an efficient synthesis of L-2′,3′-dideoxy-2′-trifluoromethyl-4′-thiocytidines **933** and **934** was also described (Scheme 139).[340] The β-trifluoromethylated lactones **901** and **902** were reduced by $NaBH_4$ to furnish the corresponding diols **927** and **928**, respectively, which, after mesylation, were treated with $Na_2S\cdot 9H_2O$ to provide the compounds **929** and **930**, respectively. Oxidation of **929** and **930** and subsequent Pummerer rearrangement produced the 1-*O*-acetates **931** and **932**, respectively. Glycosylation of the acetates **931** and **932** with silylated cytosine followed by removal of all the protecting groups delivered the target nucleosides **933** and **934**, respectively.



Scheme 137.



Scheme 138.

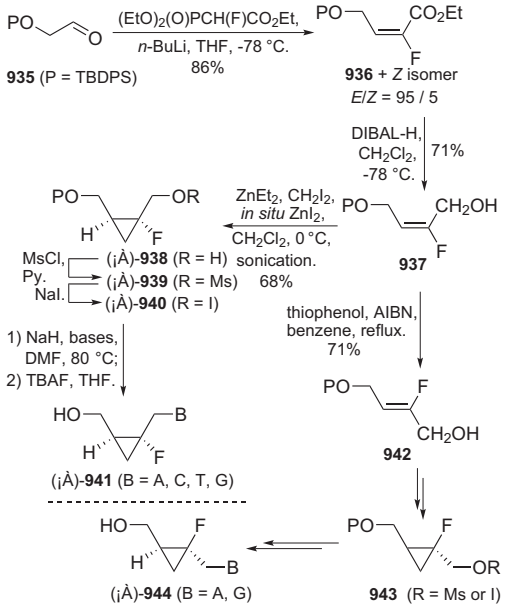


Scheme 139.

5. Other fluorinated nucleosides

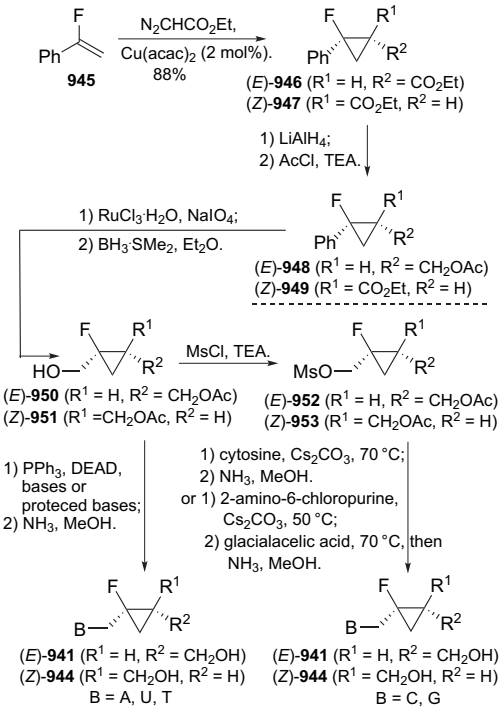
5.1. Monofluorinated or *gem*-difluorinated cyclopropane nucleosides

Kim et al. designed and synthesized some fluorocyclopropanoid nucleosides (±)-**941** in 2001.[341] As the important step of their synthetic route, introduction of fluorine and a double bond for the installation of the cyclopropyl group was actualized by an HWE reaction of the aldehyde **935** with triethyl 2-fluoro-2-phosphonoacetate using *n*-BuLi in THF (Scheme 140). After the resultant ester **936** was reduced with DIBAL-H, the obtained allylic alcohol **937** was subjected to ZnI_2-catalytic cyclopropanation to provide the cyclopropane derivative (±)-**938** in 68% yield. The alcohol (±)-**938** was converted into the corresponding mesylate (±)-**939** or iodide (±)-**940**, which were further coupled with purine or pyrimidine bases and subsequently desilylated to afford the desired cyclopropane nucleosides (*E*)-**941**. In addition, after the (*E*)-alcohol **937** was isomerized into the (*Z*)-isomer **942** by treatment with thiophenol/AIBN in refluxing benzene, the synthesis of cyclopropane nucleosides (*Z*)-**944** was also accomplished via intermediate **943** using similar reaction conditions.[342]



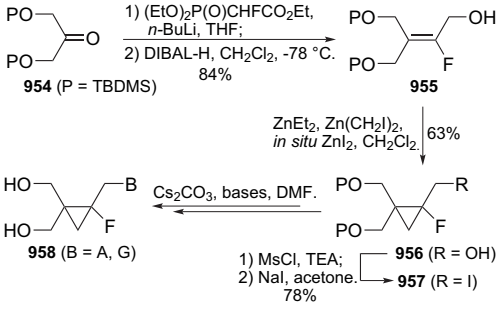
Scheme 140.

Interestingly, Haufe's group also synthesized a series of diastereopure monofluorinated cyclopropanoid nucleosides, (*E*)-**941** (B=A, U, T, C, G) and (*Z*)-**944** (B=A, U, T, C, G), using another synthetic route (Scheme 141).[343] Their method started from α-fluorostyrene **945**, which was converted into the separable esters (*E*)-**946** and (*Z*)-**947** by reaction with $N_2CHCO_2Et/Cu(acac)_2$. After reduction and O-acetylation, the resultant acetates (*E*)-**948** and (*Z*)-**949** were subjected to oxidation with $RuCl_3/NaIO_4$ and reduction with $BH_3{\cdot}SMe_2$ to afford the alcohols (*E*)-**950** and (*Z*)-**951**, respectively. Direct coupling of (*E*)-**950** and (*Z*)-**951** with the nucleobases under Mitsunobu conditions and subsequent deprotection with NH_3/MeOH provided the desired monofluorinated cyclopropanoid nucleosides (*E*)-**941** (B=A, U, T) and (*Z*)-**944** (B=A, U, T). In addition, after mesylation of (*E*)-**950** and (*Z*)-**951**, the generated mesylates (*E*)-**952** and (*Z*)-**953** were also transformed into the nucleosides (*E*)-**941** (B=C, G) and (*Z*)-**944** (B=C, G), respectively, by means of reaction with Cs_2CO_3/cytosine and Cs_2CO_3/2-amino-6-chloropurine followed by deacetylation.



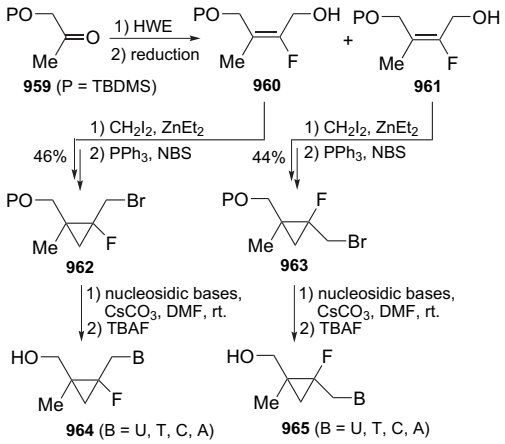
Scheme 141.

In 2003, Kim's group accomplished the synthesis of [1′-fluoro-2′, 2′-bis-(hydroxymethyl)cyclopropylmethyl]purines **958** (B=A, G).[344] Their synthesis featured the introduction of a fluorine group into the ketone **954** through an HWE reaction with $(EtO)_2P(O)CHFCO_2Et$/*n*-BuLi and cyclopropanation of the resultant allylic alcohol **955** by a Lewis acid-catalyzed Furukawa modification of the Simmons–Smith reaction (Scheme 142). Mesylation of the fluorinated cyclopropyl alcohol **956** followed by iodination gave the precursor **957** in 78% yield. Coupling of the iodide **957** with adenine or 2-amino-6-chloropurine in the presence of Cs_2CO_3 followed by desilylation (or desilylation and further treatment with $HSCH_2CH_2OH$/MeONa) provided the target nucleosides **958** (B=A, G). In addition, recently, Hong's group also carried out the synthesis of *C*-fluoro-branched cyclopropyl nucleosides **958** (B=T, U, C, A, etc.) using similar procedures.[345]



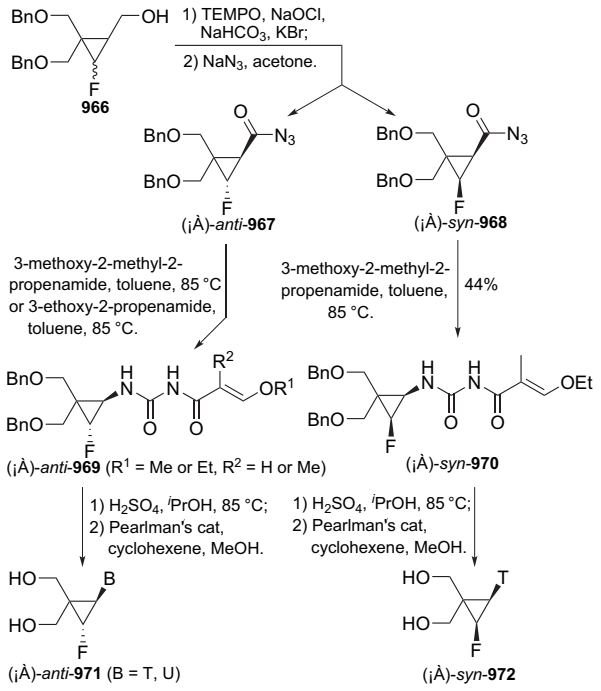
Scheme 142.

In 2007, Hong and Kim performed the synthesis of the *C*-fluoro-branched cyclopropyl nucleosides **964** and **965** (Scheme 143).[346] Their synthetic procedures were similar to those for the cyclopropyl nucleosides **958**. The major steps included the HWE reaction of compound **959**, Simmons–Smith reactions of compound **960** and **961** and introduction of nucleic acid bases via nucleophilic substitution reactions of the bromides **962** and **963**.



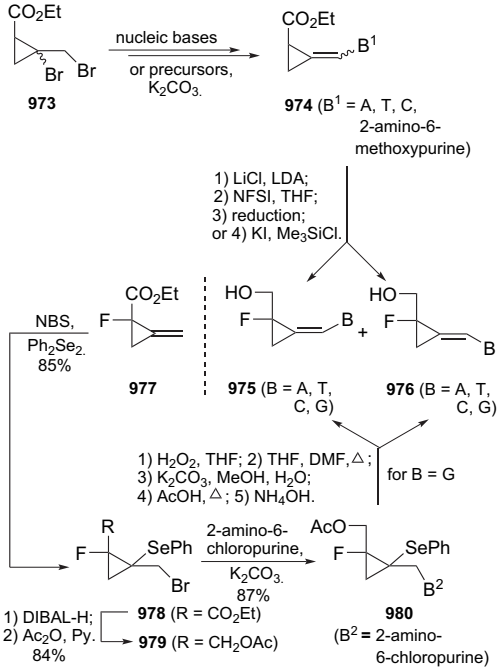
Scheme 143.

Starting from the suitably protected (fluorocyclopropyl)-methanol derivative **966**, some monofluorinated cyclopropanoid nucleosides, (±)-*anti*-**971** and (±)-*syn*-**972**, were synthesized by Csuk's group.[347] Their synthetic strategy involved the oxidation of the alcohol **966** followed by azidation with NaN_3 to afford the separable isomers, (±)-*anti*-**967** and (±)-*syn*-**968** (Scheme 144). Treatment of (±)-*anti*-**967** and (±)-*syn*-**968** with 3-methoxy-2-methyl-2-propenamide and 3-ethoxy-2-propenamide in toluene at 85 °C produced the amides (±)-*anti*-**969** and (±)-*syn*-**970**, respectively. Finally, exposure of (±)-*anti*-**969** and (±)-*syn*-**970** to H_2SO_4/^{i}PrOH and subsequent hydrogenation provided the monofluorinated cyclopropanoid nucleosides, (±)-*anti*-**971** and (±)-*syn*-**972**, respectively.



Scheme 144.

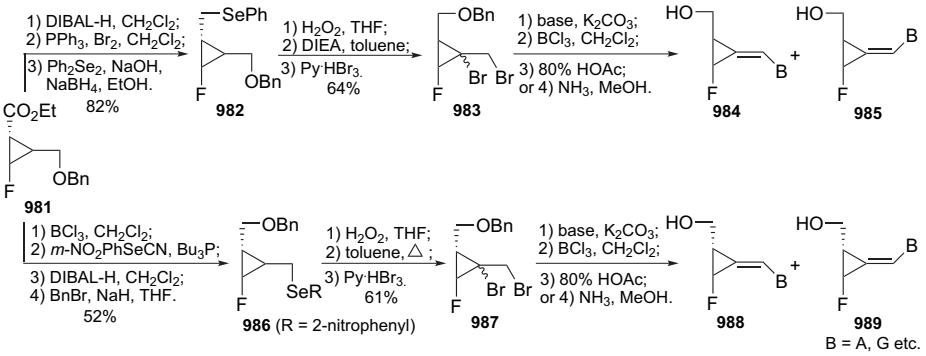
The synthesis of the *Z*- and *E*-isomers of fluoromethylenecyclopropane nucleoside analogues **975** and **976** was addressed by Zemlicka and co-workers.[348] In their synthesis, the methylenecyclopropane esters **974** were prepared by alkylation–elimination reactions between the dibromide **973** and the corresponding nucleic bases or precursors (Scheme 145). Selective monofluorination of the compounds **974** using *N*-fluorobenzenesulfonimide (NFSI) followed by reduction of the ester moiety gave the target nucleosides, (*Z*)-**975** and (*E*)-**976**. One year later, Zemlicka et al. described a new alkylation–elimination method for the synthesis of (*Z*)-**975** (B=G) and (*E*)-**976** (B=G).[349] The key steps of the new method involved phenylselenylation of the fluoroester **977** with Ph_2Se_2/NBS, alkylation of the acetate **979** with 2-amino-6-chloropurine and Se-oxidation–elimination of the intermediate **980** with H_2O_2 (then heating). Very recently, this group has also completed the synthesis of 3-fluoromethylenecyclopropane nucleoside analogues **984** and **985** and **988** and **989** from the key intermediate **981**, and the synthetic strategy also featured the alkylation–elimination reactions between the monofluorinated dibromide **983** (or **987**) and the corresponding nucleic bases or precursors (Scheme 146).[350]



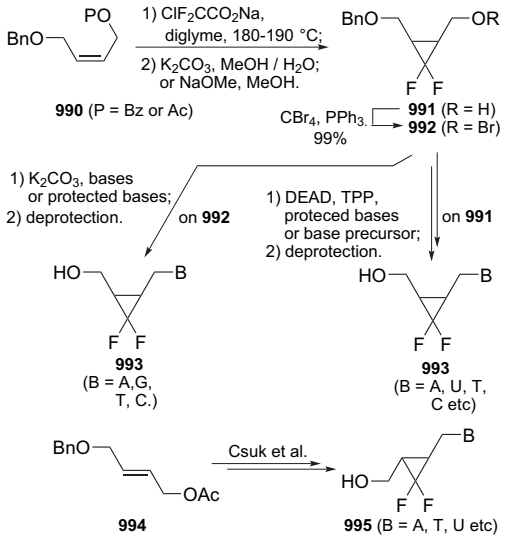
Scheme 145.

Besides the aforementioned monofluorinated cyclopropane nucleosides, Zemlicka's group and the Csuk group also carried out the synthesis of a series of difluorocyclopropyl carbocyclic nucleosides **993**, starting from the (*Z*)-2-butenyl derivatives **990** (Scheme 147).[351,352] As the key step of their synthesis, conversion of **990** into the 2,2-difluorocyclopropylmethanol **991** was realized by means of difluorocyclopropanation with $ClCF_2CO_2Na$ in diglyme at 180–190 °C followed by deacetylation or debenzoylation. At this stage, two methods were utilized to introduce the nucleic bases. One method involved Mitsunobu reactions between the alcohol **991** and the protected bases (or base precursor) followed by deprotection (and ammonolysis). The other method featured the alkylation of the nucleic acid bases with the bromide **992**, which was obtained via treatment of the compound **991** with CBr_4/PPh_3. It should be noted that Csuk's group also synthesized the *trans*-configurated difluorocyclopropyl carbocyclic nucleosides **995** from the intermediate, (*E*)-4-(benzyloxy)-2-butenyl acetate **994**, using a similar procedure.[353]

Starting from the alkene intermediate **997**, itself available through oxidation of the alcohol **996** followed by olefination with triethyl phosphonoacetate (TEPA), reduction and acetylation, the Csuk group also described an entry into the difluorinated cyclopropane nucleoside analogues **999**, which were provided by the

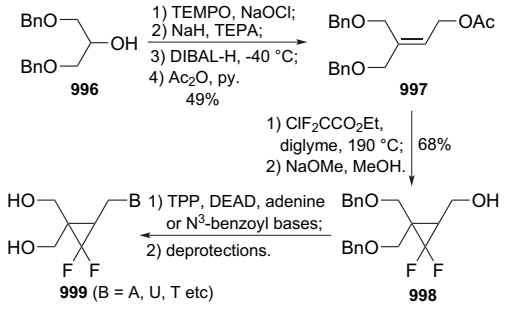


Scheme 146.



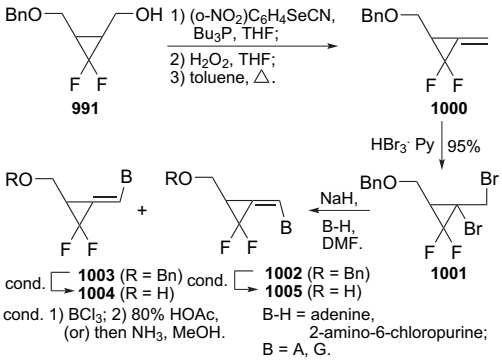
Scheme 147.

difluorocyclopropanation of the acetate **997**, deacetylation, Mitsunobu reactions between the alcohol **998** with various nucleic bases followed by two consecutive deprotection steps (Scheme 148).[354]



Scheme 148.

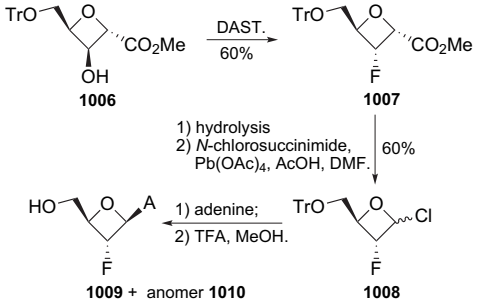
Additionally utilizing the alkylation–elimination method, Zemlicka and co-workers synthesized the methylene-*gem*-difluorocyclopropane nucleoside analogues **1004** and **1005** from the *gem*-difluorocyclopropane **991**, which was first converted into the methylene-*gem*-difluorocyclopropane **1000** in three steps (Scheme 149).[355,356] Treatment of the compound **1000** with HBr_3Py afforded the vicinal dibromocyclopropane **1001**, which underwent alkylation–elimination to produce the protected nucleosides **1002** and **1003** along with some byproducts. Removal of the benzyl groups in **1002** and **1003** with BCl_3 followed by acidic treatment gave the target nucleosides **1005** and **1004**, respectively.



Scheme 149.

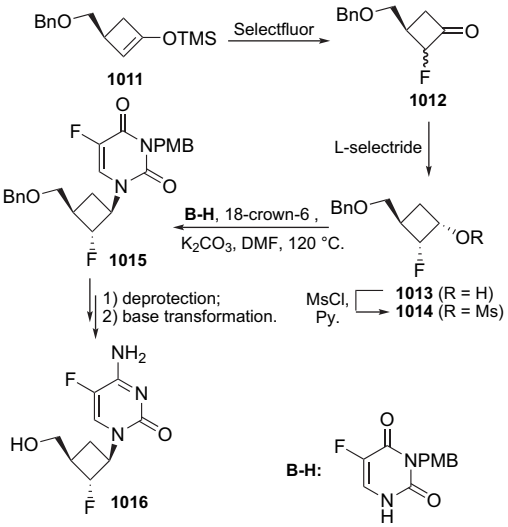
5.2. Monofluorinated or monofluoromethylated cyclobutane nucleosides

In view of the potent antiviral activity of the naturally occurring oxetane nucleoside, oxetanocin, Fleet and co-workers first accomplished the synthesis of the fluorinated oxetanocin **1009**.[357] Their synthesis was performed through DAST-mediated fluorination of the trityl-protected alcohol **1006** followed by conversion of the resultant fluorinated compound **1007** into the chlorinated product **1008** in two steps (Scheme 150). Reaction of the compound **1008** with adenine and subsequent removal of the trityl group with TFA provided the target nucleosides **1009** and its α anomer **1010**.

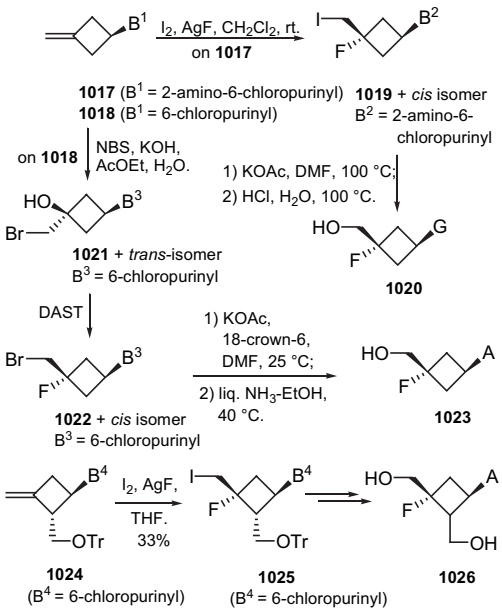


Scheme 150.

In 2007, Liotta et al. completed the synthesis of a 2′-fluoro cyclobutyl nucleoside **1016**, with fluorination of the silyl enol ether **1011** using Selectfluor as the important step (Scheme 151).[358] After reduction of the generated ketone **1012**, the resultant major isomer **1013** was mesylated to afford the compound **1014**. Coupling of the mesylate **1014** with N^3-(4-methoxybenzyl)-5-fluorouracil under basic conditions furnished the protected nucleoside **1015**, which was subjected to deprotection and base transformation to give the target fluorinated nucleoside **1016**.



Scheme 151.



Scheme 152.

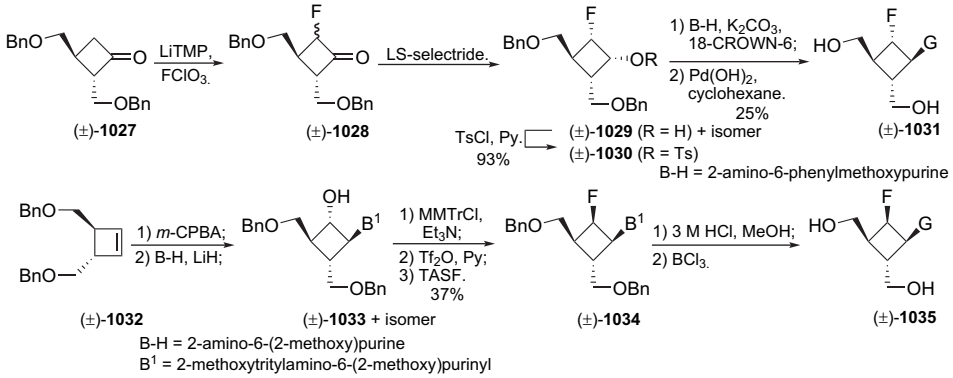
Legraverend's group realized the synthesis of the 3′-fluorocyclobutyl derivatives **1020** and **1023**, the carbocyclic analogues of oxetanocin.[359] Their synthesis featured the introduction of a 3′-fluoro atom by the direct fluoro-iodination of the olefin intermediate **1017**, or by DAST-mediated fluorination of the bromohydrin **1021** (Scheme 152). The desired nucleosides **1020** and **1023** were afforded via treatment of the iodide **1019** and the bromide **1022** with KOAc/DMF followed by acidic treatment or ammonolysis, respectively. In addition, a 3′-fluorocarbocyclic oxetanocin analogue **1026** was also synthesized, starting from the olefin **1024** and using a similar strategy, by Maruyama's group.[360]

In 1993, the synthesis of the fluorinated cyclobutane nucleoside analogues, (±)-**1031** and (±)-**1035**, was fulfilled through two different routes (Scheme 153).[361] One route was performed by the introduction of a fluorine atom adjacent to the carbonyl group of the intermediate (±)-**1027** through treatment with LiTMP/$FClO_3$. After reduction of the resultant fluorinated ketone (±)-**1028**, the generated isomer (±)-**1029** was converted into the tosylate (±)-**1030**, which was subjected to nucleophilic substitution with 2-amino-6-phenylmethoxypurine and protecting group removal to provide the cyclobutane nucleoside analogue (±)-**1031**. As for the nucleoside (±)-**1035**, the synthetic route featured the epoxidation of the cyclobutene (±)-**1031** and subsequent ring opening with 2-amino-6-methoxyethoxypurine. Conversion of the obtained alcohol (±)-**1033** into the 2′β-fluoro intermediate (±)-**1034** was accomplished by protecting the amino group and the hydroxyl group with MMTr and trifluoromethanesulfonyl, respectively, followed by TASF-mediated nucleophilic fluorine substitution. Finally, removal of all the protecting groups provided the target nucleoside (±)-**1035**.

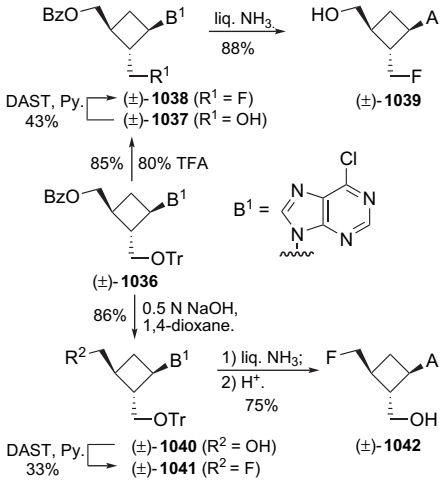
Three years later, the fluoromethyl derivatives, (±)-**1039** and (±)-**1042**, of carbocyclic oxetanocin A were synthesized, starting from the intermediate compound (±)-**1036**, which was converted into the alcohols, (±)-**1037** and (±)-**1040**, through treatment with NaOH/dioxane and with 80% TFA, respectively (Scheme 154).[362] DAST-mediated fluorination of the compounds, (±)-**1037** and (±)-**1040**, produced the fluorinated derivatives, (±)-**1038** and (±)-**1041**, respectively. The target nucleoside (±)-**1039** was provided via ammonolysis of the benzoate (±)-**1038**, and the nucleoside (±)-**1042** was obtained through ammonolysis of the compound (±)-**1041** followed by acidic treatment.

5.3. Monofluorinated or monofluoromethylated pyranyl nucleosides

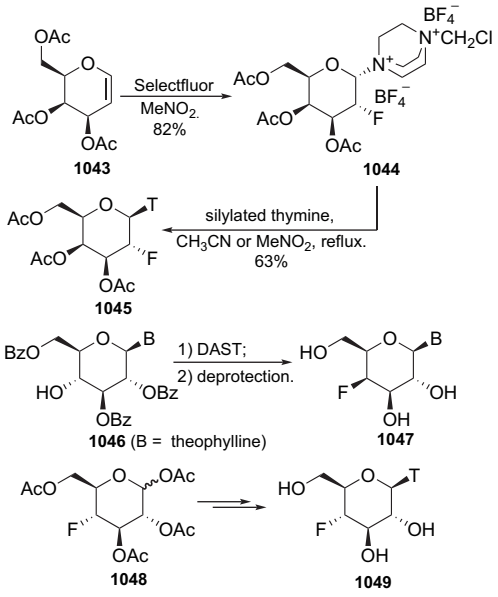
Dax et al., in 1998, described a synthetic route to 1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactopyranosyl)thymine **1045**.[363] Their method utilized the reaction between the D-galactal derivative **1043** and an electrophilic N–F reagent (Selectfluor), and the *N*-(2-deoxy-2-fluoro-glycosyl) compound **1044** was regioselectively afforded in 82% yield (Scheme 155). Subsequent treatment of the compound **1044** with silylated thymine gave the acetyl-protected 2′-



Scheme 153.



Scheme 154.

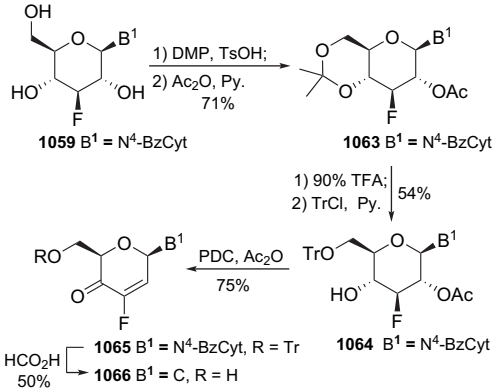


Scheme 155.

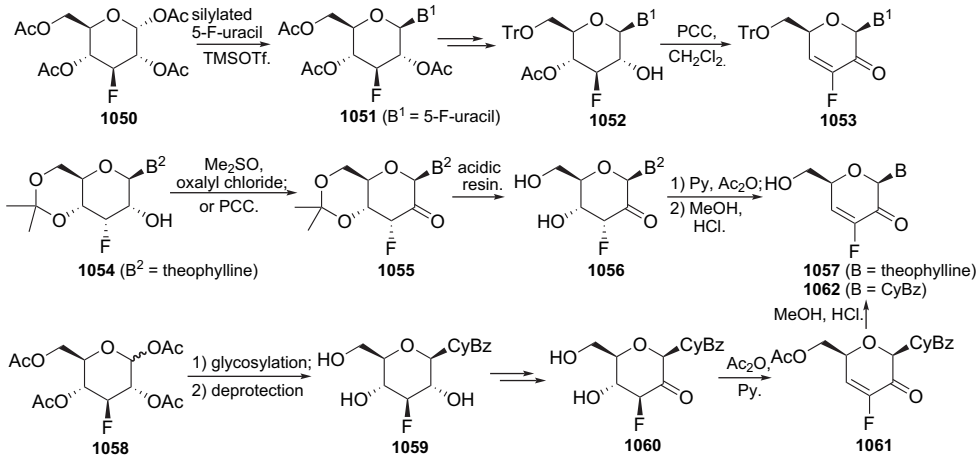
fluoro-pyranyl nucleoside **1045**. In addition, the syntheses of 4′-deoxy-4′-fluoropyranosylnucleoside anologues **1047**[364] and **1049**[365] were also accomplished by two different methods. Compound **1047** was prepared from the nucleoside derivative **1046** by fluorination followed by deprotection, while **1049** was obtained through glycosylation of the fluoro sugar **1048** and subsequent deprotection.

Starting from the peracetylated 3-deoxy-3-fluoro-α-D-glucopyranose **1050**, the synthesis of some unsaturated fluoroketo pyranucleosides was accomplished by Ollapally's group (Scheme 156).[366–368] In one of their syntheses, coupling of the compound **1050** with silylated 5-fluorouracil gave the nucleoside derivative **1051**, which was conveniently converted into the alcohol **1052** via a series of transformations of functional groups. Finally, oxidation of the compound **1052** with PDC provided the fluoroketo unsaturated nucleoside derivative **1053**. It is of interest to note that Leclercq et al. also developed another synthetic route to the unsaturated 3′-deoxy-3′-fluoroketo nucleoside derivative **1057** from the intermediate **1054** in four steps, which included oxidation of the alcohol **1054** to the ketone **1055**, removal of the isopropylidine ketal with acidic resin, treatment of the diol **1056** with Ac_2O/Py and final deacetylation.[369] Very recently, a synthesis of the fluoroketopyranosyl nucleoside **1062** was described by the Komiotis group.[370] Their synthesis involved glycosylation of the acetate **1058**, dehydration of the diol **1060** and deprotection of the resultant acetate **1061**.

It should be noted that, commencing from the intermediate **1059**, Komiotis also synthesized and biologically evaluated the unsaturated 3-fluoro-4-keto-β-D-glucopyranosyl nucleoside **1066** (Scheme 157).[371] Isopropylidination of **1059** and subsequent acetylation of the remaining hydroxyl group gave the acetyl derivative



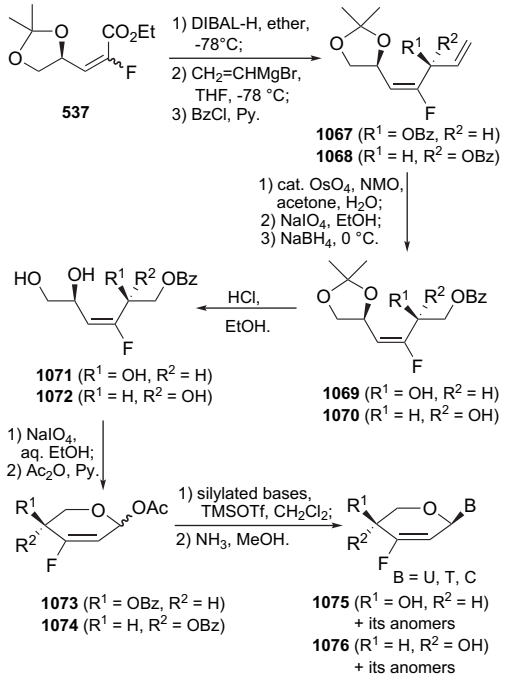
Scheme 157.



Scheme 156.

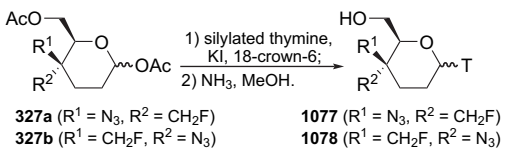
1063 in 71% yield, which was subjected to *de*isopropylidination with TFA and selective protection with a trityl group to yield the alcohol **1064**. PDC oxidation followed by in situ β-elimination provided the unsaturated 3-fluoro-4-keto-β-D-glucopyranosyl derivative **1065** in 75% yield. Final removal of the trityl group with HCO_2H gave the target nucleoside **1066**.

Starting from the α-fluoro-α,β-unsaturated ester **537**, Chu's group accomplished the synthesis of a series of fluorinated pyranosyl nucleosides in D- and L-configurations.[372] In their synthesis, conversion of the compound **537** into the separable diastereoisomers **1067** and **1068** was realized through reduction with DIBAL-H, Grignard reactions of the generated α,β-unsaturated aldehydes with CH_2=CHMgBr and subsequent benzoylation (Scheme 158). Dihydroxylation of **1067** and **1068** followed by $NaIO_4$-mediated oxidation and reduction with $NaBH_4$ gave the benzoyl-migrated alcohols **1069** and **1070**, respectively. After removal of the isopropylidine ketals in the compounds **1069** and **1070**, the resultant triols **1071** and **1072** were further subjected to oxidation with $NaIO_4$ and acetylation to afford the unsaturated pyranosyl derivatives **1073** and **1074**, respectively. Finally, N-glycosylation of the pyranosyl acetates **1073** and **1074** with silylated bases under Vorbrüggen conditions gave the corresponding protected nucleosides, which were converted into the target nucleosides **1075** (+ anomers) and **1076** (+ anomers) after deprotection, respectively.



Scheme 158.

Ton-That described the synthesis of 2′,3′,4′-trideoxypyranosylnucleoside analogues **1077** and **1078** from the acetates **327a** and **327b**, respectively, i.e., condensation of the compounds **327a** and **327b** with silylated thymine followed by deacetylation with NH_3/MeOH gave the target nucleosides **1077** and **1078**, respectively (Scheme 159).[177]

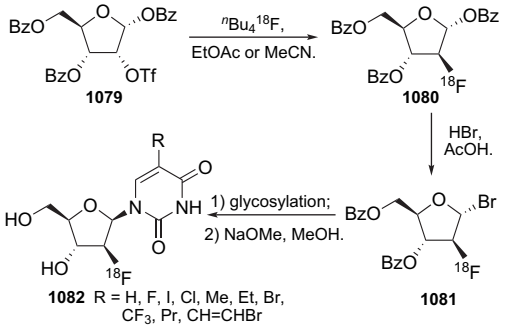


Scheme 159.

6. ^{18}F-containing nucleosides

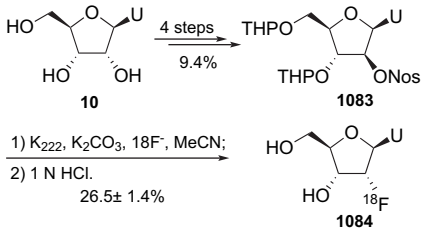
Positron emission tomography (PET) is a non-invasive imaging technology, which provides a unique window on the physiology and function of living organisms with the highest sensitivity and resolution.[373–375] To date, PET plays an important role in drug discovery by validating the mechanism of drug localization, establishing the transport efficiency of a drug to the target, addressing the drug occupancy of the saturable receptor sites and determining the half life of occupancy of the drug. PET uses short-lived positron-emitting isotopes to trace labelled compounds in vivo. The most commonly used isotopes are ^{11}C, ^{18}F, ^{15}O, ^{13}N, ^{76}Br and ^{124}I. Due to the short half lives of ^{11}C ($t_{1/2}$=20 min), ^{15}O ($t_{1/2}$=2 min) and ^{13}N ($t_{1/2}$=10 min), and the longer half lives of ^{76}Br ($t_{1/2}$=16 h) and ^{124}I ($t_{1/2}$=4.28 days), which limit their clinical applications, labelling with the medium longer-lived PET isotope of ^{18}F ($t_{1/2}$=110 min) is of considerable advantage. During the past decade, many radiolabeled ^{18}F-containing nucleosides were identified as potential PET imaging agents for tumour proliferation and gene expression. Accordingly, a large number of synthetic strategies concerning precursor design, labelling conditions and deprotection of the intermediate compounds were developed to guarantee an efficient high radiochemical yield for PET use.

Conti and Blasberg et al. developed an efficient procedure to synthesize the 2′β-[^{18}F]fluoro-*arabino* nucleosides **1082**.[376–381] Their synthesis featured that the ^{18}F intermediate **1080** was prepared in 32–68% yield via treatment of the 2-sulfonate ester **1079** with $^{n}Bu_4{}^{18}F$ (in situ prepared from $^{n}Bu_4HCO_3$ and aqueous H^{18}F) in EtOAc or MeCN (Scheme 160). Bromination of the product **1080** with HBr/AcOH at 80–82 °C gave the ^{18}F-labelled bromo sugar **1081**. Coupling of **1081** with a series of silylated thymine derivatives and subsequent removal of the Bz groups with NaOMe/MeOH provided the target [^{18}F]-containing nucleosides **1082** and their α isomers. In addition, Mangner and co-workers reported that the ^{18}F intermediate **1080** could also be accessed via treatment of the triflate **1079** and 2-*O*-(imidazolylsulfonyl)-1,3,5-tri-*O*-benzoyl-α-D-*ribo*-furanose with [^{18}F]fluoride/KHF_2 and [^{18}F]fluoride/K_{222}/K_2CO_3, respectively.[382]



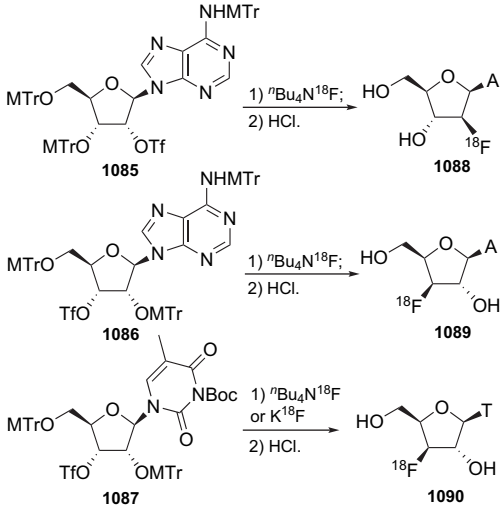
Scheme 160.

2′-Deoxy-2′α-[^{18}F]fluorouridine **1084** was synthesized by Oh and co-workers in 2006 (Scheme 161).[383] The key nosylate precursor **1083** was prepared, with an overall yield of 9.4%, from uridine **10** in four steps. Oh et al. found that the [^{18}F]fluorination yields of the nosylate **1083** depended on the reaction temperature and the precursor concentration. The optimal [^{18}F]fluorination conditions were 30 mg of precursor **1083** at 145 °C for 15 min with 370 MBq of [^{18}F]fluoride. After removal of the protecting groups with 1 N HCl and purification by HPLC, the overall radiochemical yield and purity were up to 26.5±1.4 and 98.2±2.5%, respectively.



Scheme 161.

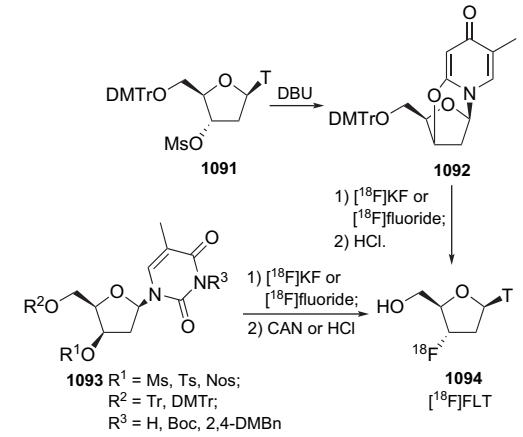
By means of [^{18}F]fluorination of the premodified triflates **1085**–**1087**, Allauddin et al. carried out the synthesis of [^{18}F]-labelled adenosine analogues **1088** and **1089** and 3′-deoxy-3′-[^{18}F]fluoro-1-β-D-*xylo*-furanosyluracil **1090** (Scheme 162).[384,385] Either $Bu_4N^{18}F$ or $K^{18}F$ could be used as the fluorinating agent, although, $Bu_4N^{18}F$ has advantages in view of its good solubility in organic solvents and low reaction temperature. The radiochemical yields were 10–18% decay corrected (d.c.) for **1088** in 4 runs, 30–40% (d.c.) for **1089** in 3 runs and 25–40% (d. c.) for **1090** in 4 runs. All the radiochemical purities were >99% and the specific activity was >74 GBq/μmol at the end of the synthesis.



Scheme 162.

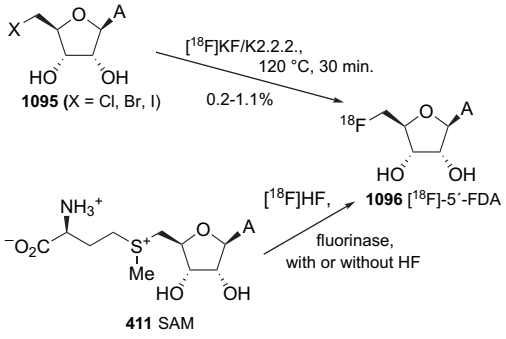
Two types of precursors were utilized to synthesize 3′-deoxy-3′-[^{18}F]fluorothymidine **1094** ([^{18}F]FLT) (Scheme 163). One precursor was 2,3′-anhydro-5′-*O*-(4,4′-dimethoxytrityl)thymidine **1092**,[386,387] which was prepared via treatment of the mesylate **1091** with DBU. Using [^{18}F]KF/K2.2.2 as the labelling agent in DMSO at 175 °C for 1 h, Eisenhut's group found that [^{18}F]FLT could be obtained in a radiochemical yield of 5.6±1.4% after deprotection. It is of interest to note that Machulla et al. demonstrated that the labelling of **1092** with $KHCO_3$/[^{18}F]fluoride/K2.2.2 proceeded well within 30 min in radiochemical yields of almost 20% when the reaction was carried out in polar solvents such as DMF or DMSO at 160 °C. The other types of precursors were the mesylated, tosylated and nosylated derivatives **1093**.[388–392] Treatment of these compounds with [^{18}F]fluorinating agents followed by removal of the protecting groups gave the [^{18}F]FLT. It was shown that the nosylated precursors were more favourable for radiofluorination than the mesylated or tosylated derivatives. Additionally, a positive effect on the radiochemical yield was also found with DMTr in comparison to Tr as protecting group at the 5′-*O*-position.

In 2000, Trón's group investigated the reactions of 5′-deoxy-5′-haloadenosines **1095** with [^{18}F]KF/K2.2.2 and found that halogen



Scheme 163.

exchange reactions did take place to some extent, although the conversions were rather low (0.2–1.1%) (Scheme 164).[393] Three years later, Martarello and O'Hagan et al. carried out the fluorinase-catalytic preparation of 5′-[^{18}F]fluoro-5′-deoxyadenosine **1096** ([^{18}F]-5′-FDA) by incubating a protein extract from *S. cattleya* with [^{18}F]HF and SAM **411**.[394] Their study demonstrated that a radiolabelling reaction occurred when the concentration of the enzyme preparation was increased from sub-mg/ml values to mg/ml values. In addition, they also found that the purity of the enzyme had no measurable effect on the radiochemical yield and the radiochemical purity of [^{18}F]-5′-FDA.



Scheme 164.

7. Conclusions

In this review, we have systematically presented the recent advances in the synthesis of fluorinated nucleosides and it is evident that tremendous progress has been made in the past few years. Clearly, two main tactics have been employed for the synthesis of fluorinated nucleosides. One startegy has featured the installation of fluorine atom(s) into pre-modified precursor compounds before the introduction of nucleic bases. Alternatively, the second strategy has involved the regio- or stereoselective introduction of fluorine atom(s) into suitablely modified nucleoside derivatives. No matter which approach is utilized, developing novel short-step, large-scale synthetic routes to fluorinated nucleosides, especially some well-known highly bioactive fluorinated nucleosides, remains a continuous and significant challenge. In addition, it is also important that methods should be developed for the combinatorial library synthesis of fluorinated nucleosides. As for designing novel fluorinated nucleosides, the emphasis should focus on structure-based computational methods and tools for

substrate–target interactions. In the next few years, we are likely to see some new and exciting syntheses of fluorinated nucleosides in the endeavours to develop novel anti-cancer and anti-virus nucleoside analogues. Thus, we hope that, with this review, we have provided an appropriate background for such developments to take place and an encouragement to organic chemists to pursue the synthesis of fluorinated nucleosides.

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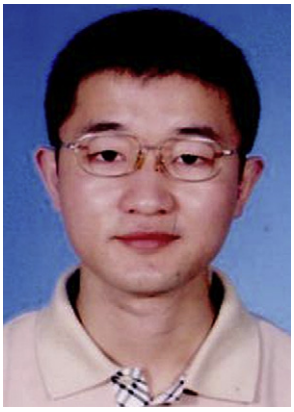

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