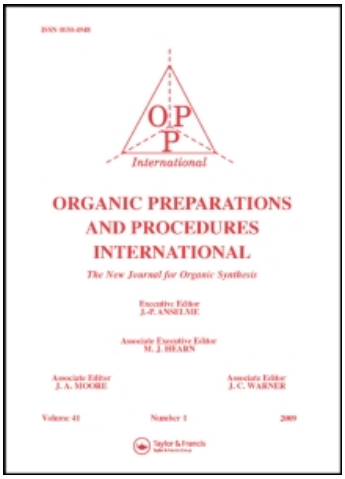

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Online publication date: 28 May 2010

To cite this Article Li, Nan-Sheng , Lu, Jun and Piccirilli, Joseph A.(2010) 'Synthesis of 2'-*C*-Branched Nucleosides', Organic Preparations and Procedures International, 42: 3, 191 — 283
To link to this Article: DOI: 10.1080/00304948.2010.483657
URL: http://dx.doi.org/10.1080/00304948.2010.483657

Organic Preparations and Procedures International, 42:191–283, 2010

ISSN: 0030-4948 print
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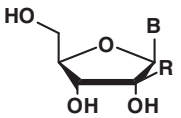
Introduction

Since Walton *et al.* reported in 1966 that 2′-*C*-methyladenosine is resistant to adenosine deaminase and exhibits inhibitory activity against KB cells in culture,[1,2] significant attention has been devoted to the synthesis and biological studies of nucleosides bearing 2′-branched-chain sugars. A number of 2′-*C*-branched nucleosides have displayed promising anticancer[3–13] and antiviral activities.[14] For example, 2′-*C*-methylpurine and 2′-*C*-methylpyrimidine nucleosides have shown inhibitory activity against RNA virus replication.[15–20] The 2′-*C*-branched nucleosides have also been used as biochemical probes to address nucleic acid structure and function relationships.[21–26] The synthesis of 2′-*C*-branched nucleosides has not been reviewed previously. The present review covers a period from 1966 to 2009. *Figure 1* summarizes structural classes of 2′-*C*-branched nucleosides prepared in literature and reviewed here. The references are organized into five sections and discussed in the following order: I. 2′-*C*-Branched Ribonucleosides; II. 2′-*C*-Branched Arabinonucleosides and 2′-*C*-Methylenenucleosides; III. 2′-*C*-β-Branched-2′-deoxynucleosides; IV. 2′-*C*-α-Branched-2′-deoxynucleosides; V. Conformationally Locked 2′-Branched Nucleosides.

I. 2′-*C*-Branched Ribonucleosides



2′-*C*-β-Branched ribonucleosides are generally prepared *via* two synthetic methods. One is the convergent approach, where the nucleobase is glycosylated with the appropriated modified sugar, and the other is a linear approach starting from the unmodified

Received September 15, 2009; accepted March 16, 2010.

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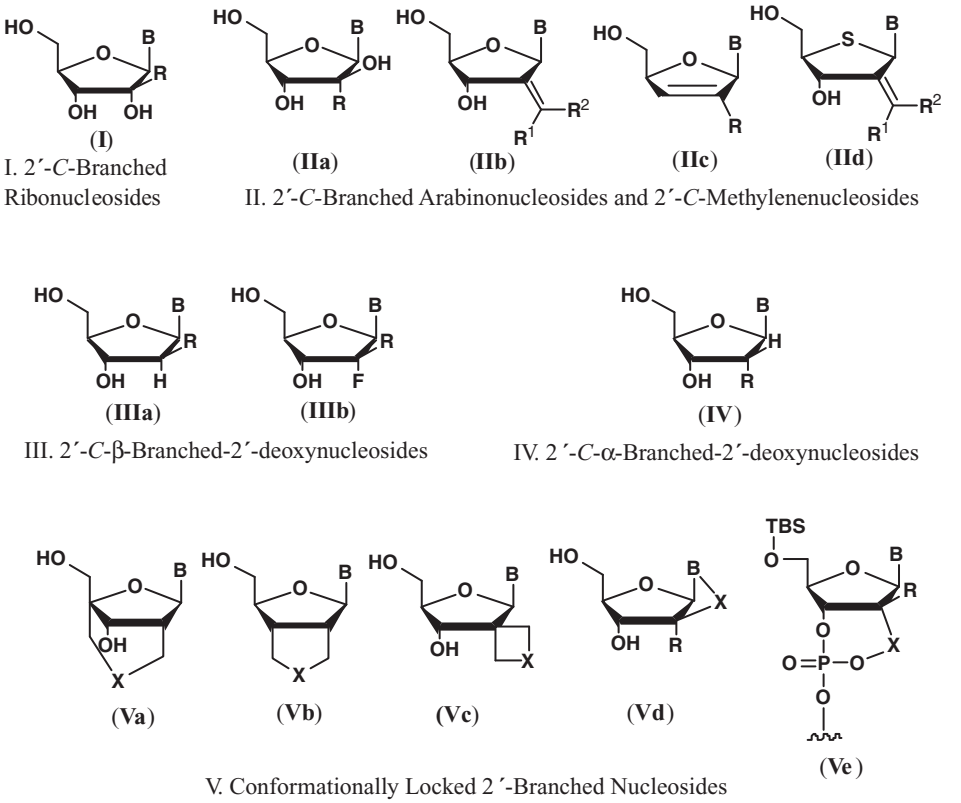
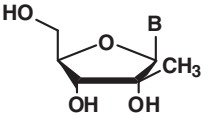


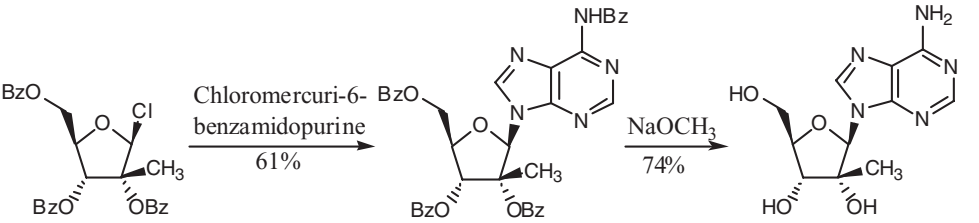
Figure 1
Structure classes of 2′-*C*-branched nucleosides.

nucleoside. The linear approach offers a relatively rapid route to 2′-*C*-branched nucleosides; however, it offers the corresponding 2′-alkylribonucleosides as minor products. Specifically, *via* reaction of 2′-ketonucleoside derivatives with organometallics, the diastereomeric 2′-alkylarabinonucleosides are usually the major products (the synthesis of 2′-alkylarabinonucleosides is discussed in *Section II* of this review). Compared with the linear approach, the convergent approach is potentially more flexible because a variety of nucleobases can be coupled to the modified sugar. Therefore, 2′-*C*-branched ribonucleosides are mainly synthesized by the convergent approach. Below, we review the reported syntheses of 2′-*C*-branched ribonucleosides and in some cases the corresponding phosphoramidites.

1. 2′-C-β-Methyl Ribonucleosides



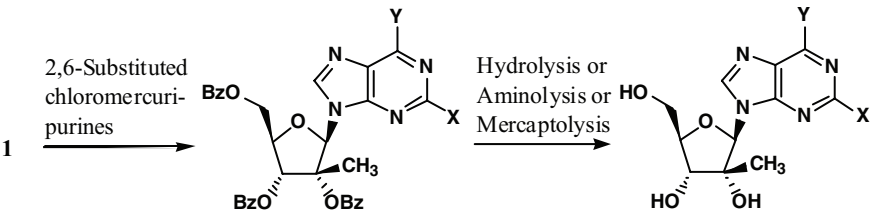
2′-*C*-β-Methyl ribonucleosides were mainly prepared by the glycosylation of various nucleobases with 2-β-methylribose derivatives. In the 1960s, Walton *et al.* first reported the synthesis of 2′-*C*-β-methyladenosine by glycosylation of 2,3,5-tri-*O*-benzoyl-2-*C*-methyl-β-D-ribofuranosyl chloride (**1**).[1,27] The 1-chloro sugar **1** was prepared from 2-*C*-β-methyl-D-ribono-γ-lactone in four steps *via* benzoylation, reduction, re-benzoylation and chlorination,[27] and then reacted with chloromercuri-6-benzamidopurine to give the perbenzoylated nucleoside **2a** in 61% yield (*Scheme 1*). Removal of the benzoyl blocking groups with sodium methoxide in methanol led to the isolation of 2′-*C*-β-methyladenosine (**3a**) in 74% yield.



1 **2a** **3a**

Scheme 1

In a 1968 patent,[28] Walton further described the reaction of **1** with six chloromercuripurines to give 2′,3′,5′-*O*-tribenzoylpurine nucleosides (**2a–f**) (*Scheme 2*). The benzoyl protected purine nucleosides (**2a–f**) were hydrolyzed, aminolyzed, or mercaptolyzed to produce eleven 2′-*C*-β-methyl purine nucleosides (**3a–k**).

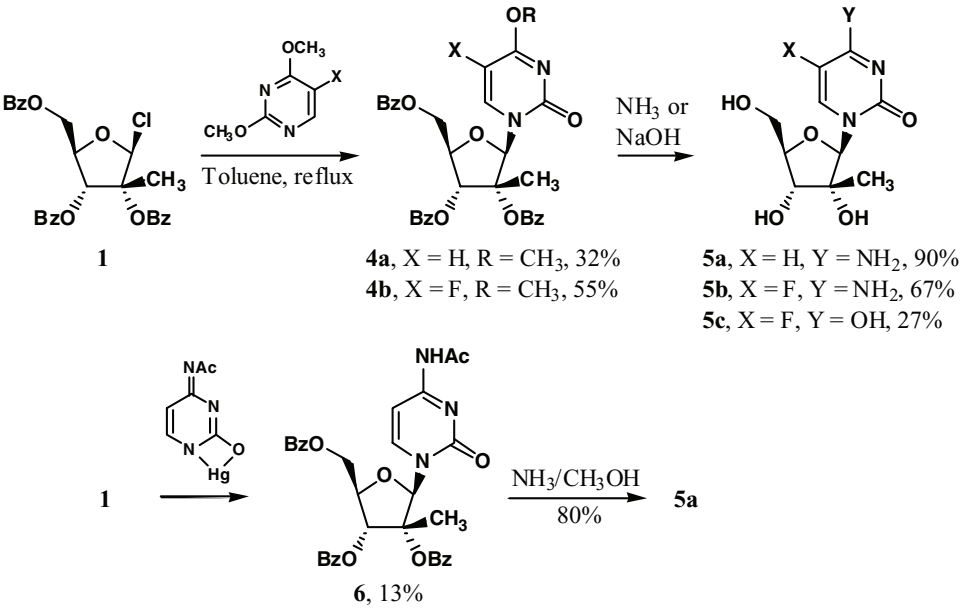


2a: X = H, Y = NHBz
2b: X = AcNH, Y = OH
2c: X = H, Y = NMeBz
2d: X = H, Y = Cl
2e: X = Y = BzNH
2f: X = H, Y = Me

3a: X = H, Y = NH_2
3b: X = NH_2, Y = OH
3c: X = H, Y = NHMe
3d: X = H, Y = Cl
3e: X = Y = NH_2
3f: X = H, Y = Me
3g: X = H, Y = NMe_2
3h: X = H, Y = NHEt
3i: X = H, Y = SH
3j: X = H, Y = SMe
3k: X = Y = H

Scheme 2

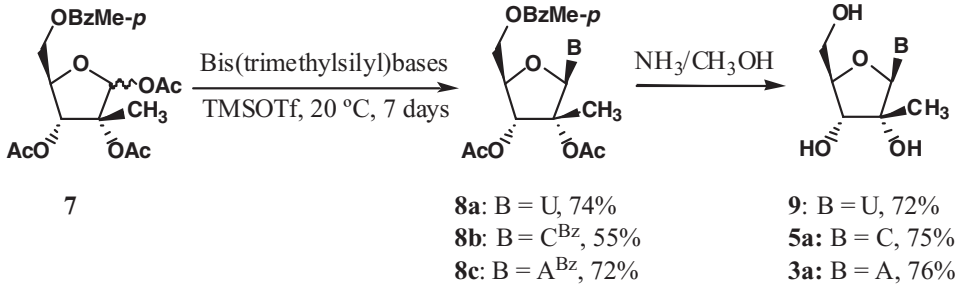
Walton also reported the synthesis of 2′-*C*-β-methyl pyrimidine nucleosides (*Scheme 3*).[2] Reaction of **1** with 2,4-dimethoxypyrimidine or 2,4-dimethoxy-5-fluoropyrimidine in dry toluene at reflux for 5 days produced the corresponding coupling products **4a** or **4b** in 32% and 55% yields, respectively. Treatment of **4a** or **4b** with ammonia gave 2′-*C*-β-methylcytidine (**5a**) or 2′-*C*-β-methyl-5-fluorocytidine (**5b**) in 90% and 67% yields, respectively. Hydrolysis of **4b** with sodium hydroxide generated 2′-*C*-β-methyl-5-fluorouridine



Scheme 3

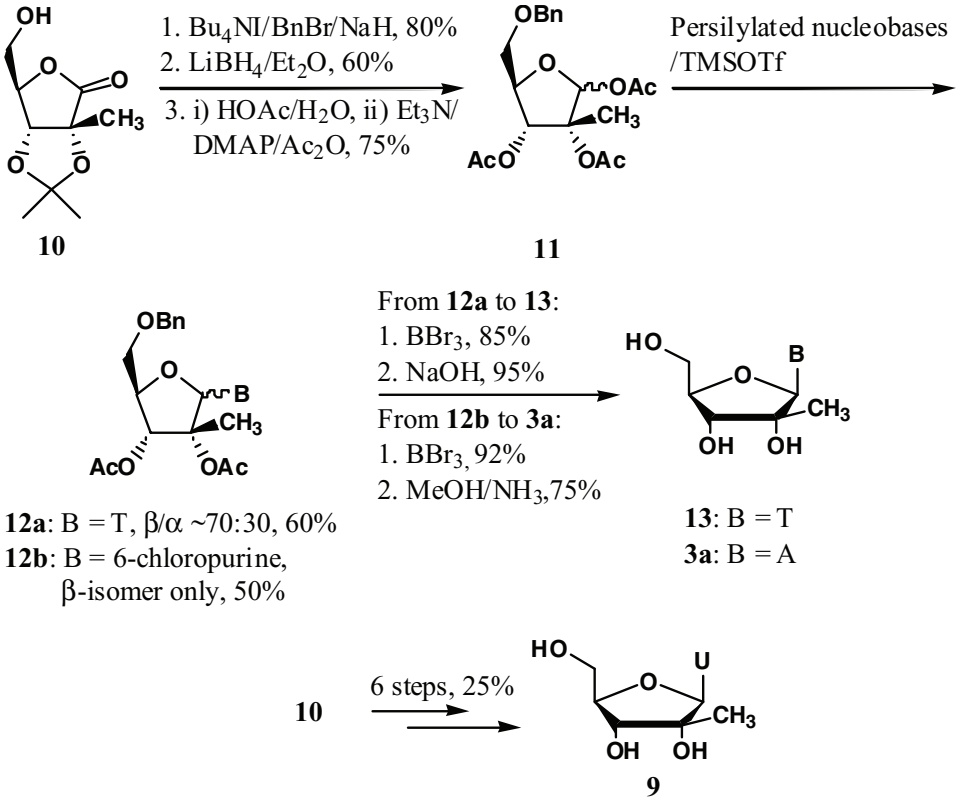
(**5c**) in 27% yield. Alternately, the reaction of **1** with the mercury (II) complex of N^4-acetylcytosine gave N^4-acetyl-2′,3′,5′-tri-*O*-benzoyl-2′-*C*-methyl-β-D-cytidine (**6**) but in low yield (13%). Hydrolysis of **6** with ammonia gave 2′-*C*-β-methylcytidine (**5a**) in 80% yield.

In 1987, Beigelman reported the synthesis of both 2′-*C*-β-methylpyrimidine and 2′-*C*-β-methylpurine nucleosides by glycosylation with 1,2,3-tri-*O*-acetyl-2-*C*-β-methyl-5-*O*-*p*-methylbenzoyl-D-ribofuranose (**7**) (*Scheme 4*).[29] The glycosylating reagent (**7**) was prepared either from D-glucose or from D-ribose in 11 steps. Glycosylation of persilylated uracil, N^4-benzoylcytosine, and N^6-benzoyladenine with **7** in the presence of TMSOTf gave glycosylation products **8a–c** in 55–72% yield. Removal of the acetyl and methylbenzoyl groups from **8a–c** with ammonia yielded the corresponding 2′-*C*-methylnucleosides: 2′-*C*-β-methyluridine (**9**), 2′-*C*-β-cytidine (**5a**) and 2′-*C*-β-adenosine (**3a**) in 72%, 75% and 76% yields, respectively (*Scheme 4*).



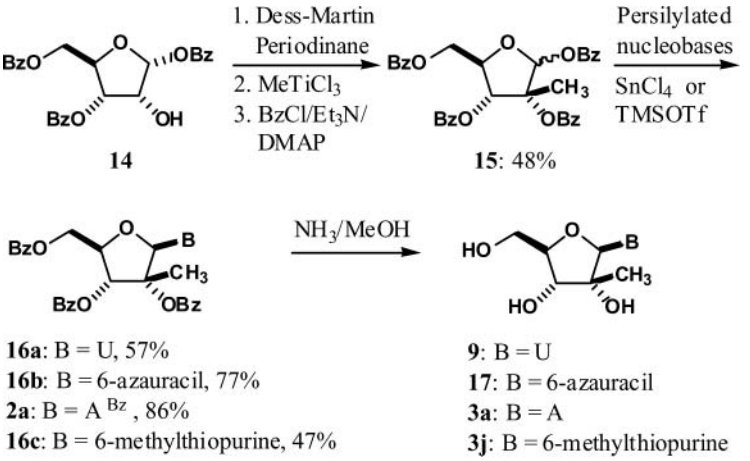
Scheme 4

Similarly, Wolf synthesized 2′-*C*-β-methyl-5-methyluridine (**13**) and 2′-*C*-β-methyladenosine (**3a**) by the glycosylation of nucleobases with 1,2,3-tri-*O*-acetyl-5-*O*-benzyl-2-*C*-β-methyl-D-ribofuranose (**11**) (*Scheme 5*).[30] The glycosylating agent **11** was prepared in four steps from 2,3-*O*-isopropylidene-*C*-β-methyl-D-ribono-γ-lactone (**10**) with 36% overall yield. Glycosylation of *N*-trimethylsilyl-6-chloropurine with **11** gave the β-isomer of 6-chloropurine nucleoside derivative **12b** exclusively (50% yield). However, glycosylation of bis(trimethylsilyl)thymine with **11** gave a mixture of α and β-anomers of 2′-*C*-β-methylthymidine derivative (**12a**) (β/α ~70:30) in 60% yield. The isomers of **12a** were inseparable at this stage but were separable after 5′-debenzylation with boron tribromide. Debenzylation of **12a** and **12b** with boron tribromide followed by sodium hydroxide or ammonia treatment afforded 2′-*C*-β-methyl-5-methyluridine (**13**) and 2′-*C*-β-methyladenosine (**3a**) in good yields. 2′-*C*-β-Methyluridine (**9**) was also prepared from **10** in six steps with 25% overall yield.[31]



Scheme 5

A widely used glycosylating reagent: 1,2,3,5-tetra-*O*-benzoyl-2-β-methylribofuranose (**15**) was prepared from 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**14**) by Harry-O'Kuru *et al.* in three steps (*Scheme 6*).[32–34] Compound **14** was oxidized to a ketone by Dess-Martin Periodinane in high yield. Addition of methyltrichlorotitanium to the ketone followed by benzoyl protection gave perbenzoylated 2-β-methylribofuranose (**15**) in 48% overall yield. Glycosylation of persilylated bases with **15** in the presence of $SnCl_4$ (for



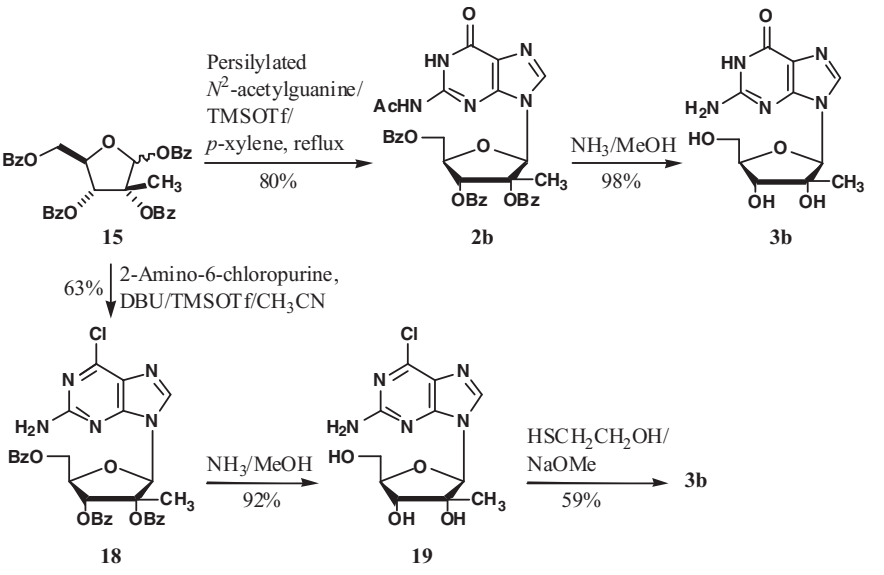
Scheme 6

pyrimidines) or trimethylsilyl triflate (for purines) gave perbenzoylated 2′-*C*-*β*-methylnucleoside derivatives **16a**, **16b**, **2a**, or **16c** in 47–86% yield. Deprotection with saturated ammonia in methanol gave 2′-*C*-*β*-methyluridine (**9**), 2′-*C*-*β*-methyl-6-azauridine (**17**), 2′-*C*-*β*-methyladenosine (**3a**), and 2′-*C*-*β*-methyl-6-methylthiopurine nucleoside (**3j**) in good yields.

Recently we extended Harry-O'Kuru's approach to the synthesis of 2-*C*-*β*-methylguanosine (**3b**) by glycosylation of persilylated N^2-acetylguanine with **15**. The reaction was carried out in refluxing *p*-xylene to give intermediate **2b** in 80% yield. Deprotection of **2b** with ammonia gave 2′-*C*-*β*-methylguanosine (**3b**) in 98% yield (*Scheme 7*).[35,36] Eldrup *et al.* also reported the synthesis of 2′-*C*-*β*-methylguanosine (**3b**) by glycosylation of 2-amino-6-chloropurine with **15** in the presence of DBU and trimethylsilyl triflate. Glycosylation followed by two hydrolysis steps (debenzoylation with ammonia and dechlorination with $HSCH_2CH_2OH$/NaOMe) gave **3b** in 34% overall yield (*Scheme 7*).[20]

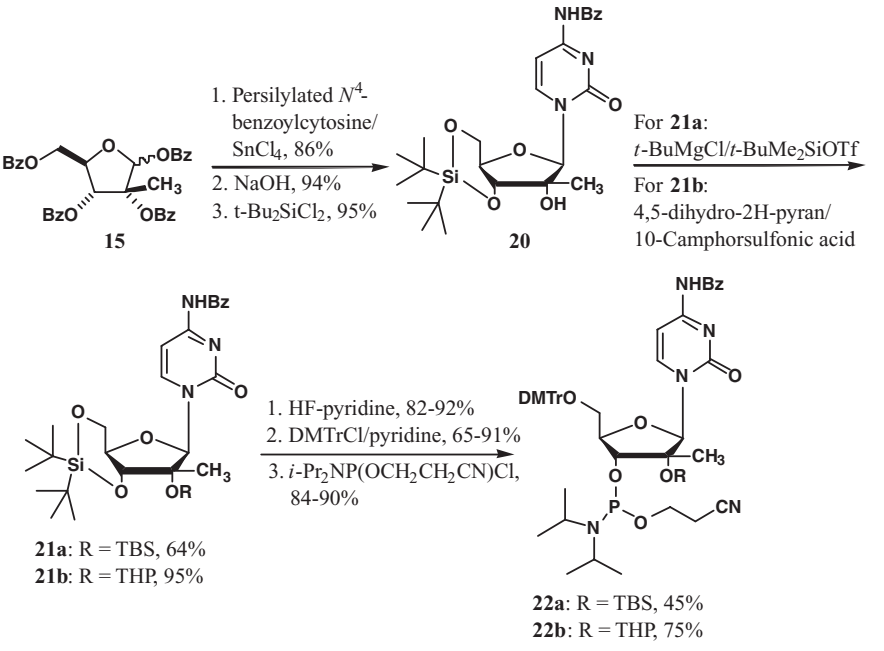
To incorporate 2′-*C*-*β*-methylcytidine into oligonucleotides, Tang *et al.* synthesized the phosphoramidite derivatives of 2′-*C*-*β*-methylcytidine (**22a** and **22b**) (*Scheme 8*).[37] Glycosylation of persilylated N^4-benzoylcytosine with **15** followed by selective removal of the benzoyl groups and selective 3′,5′-*O*-di-*tert*-butylsilanediyl protection gave 2′-*C*-*β*-methylcytidine derivative **20** in 77% overall yield. The 2′-hydroxyl group of 2′-*C*-*β*-methylcytidine derivative **20** was protected by a TBS group with *t*-BuMgCl/*t*-$BuMe_2SiOTf$ or by a THP group with 4,5-dihydro-2H-pyran/10-camphorsulfonic acid to give **21a** and **21b** in 64% and 95% yields, respectively. **21a** and **21b** were then converted into the corresponding phosphoramidite derivatives: **22a** and **22b** in three steps (selective 3′,5′-desilylation, 5′-DMTr protection and 3′-phosphitylation) with 45% and 75% overall yields, respectively.

The phosphoramidite derivative of 2′-*C*-*β*-methyl-2′-*O*-THP-uridine was also synthesized *via* a linear approach from uridine by Gallo *et al.* (*Scheme 9*).[38] The 3′,5′-*O*-tetraisopropyldisiloxane-1,3-diyl uridine (**23**) was converted into a 2′-*C*-*β*-hydroxymethyluridine derivative **24** in four steps (oxidation to 2′-ketouridine, Wittig reaction to 2′-methyleneuridine, OsO_4 oxidation to a diol, and selective primary alcohol

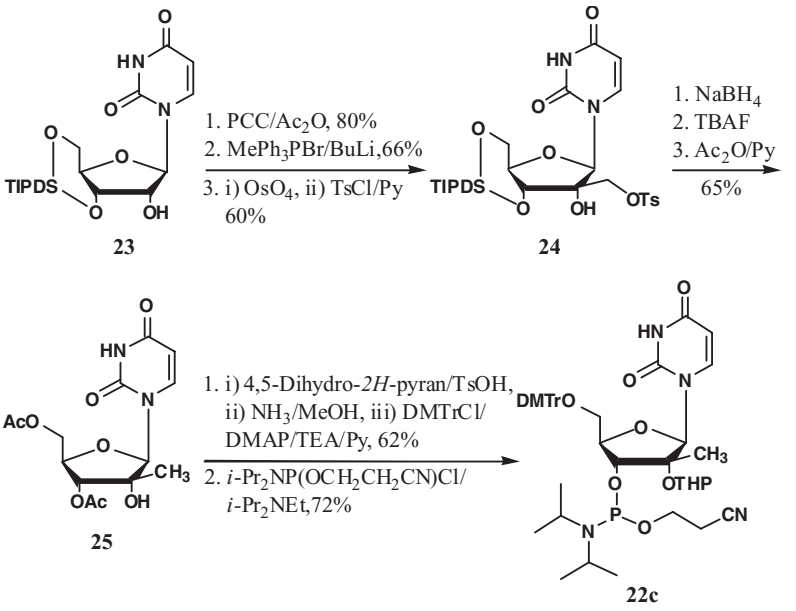


Scheme 7

tosylation) with 32% overall yield. Reduction of **24** followed by desilylation and selective acetylation gave 3′,5′-di-*O*-acetyl-2′-*C*-β-methyluridne (**25**) in 65% yield. Compound **25** was then converted into the 2′-*C*-β-methyl-2′-*O*-THP-uridine phosphoramidite (**22c**) in four steps with 45% overall yield.

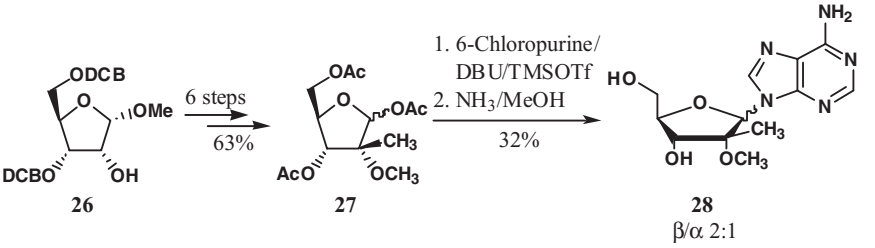


Scheme 8



23 **24** **25** **22c**

Scheme 9

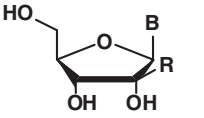


26 **27** **28**
β/α 2:1

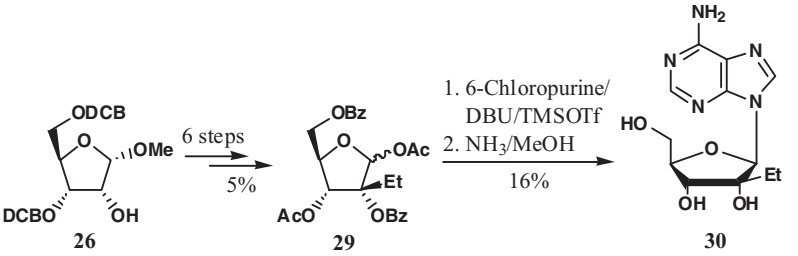
Scheme 10

The 2′-*O*-methyl-2′-*C*-*β*-methyl ribonucleoside: 2′-*O*-methyl-2′-*C*-*β*-methyl adenosine (**28**) was prepared by Eldrup *et al.* from methyl 3,5-di-*O*-dichlorobenzylribofuranoside (**26**) (*Scheme 10*).[20] The partially benzyl protected ribofuranoside (**26**) could be prepared from (D)-ribose and converted into 1,3,5-tri-*O*-acetyl-2-*O*-methyl-2-*C*-*β*-methylribose (**27**) in 63% overall yield (six steps). Glycosylation of 6-chloropurine with **27** in the presence of TMSOTf and DBU, followed by aminolysis gave a mixture of *β*/*α* anomers of 2′-*O*-methyl-2′-*C*-*β*-methyladenosine (**28**) in 32% yield (*β*/*α* ~2:1).

2. 2′-C-β-Ethyl-, Vinyl- and Ethynylribonucleosides



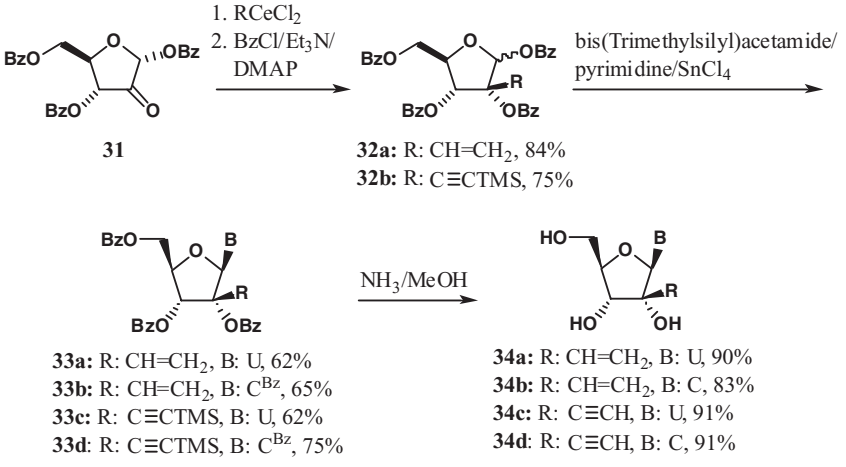
R = Et, CH_2=CH, HC≡C



Scheme 11

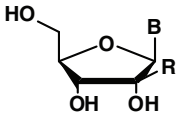
The 2′-*C*-*β*-ethyl, vinyl and ethynyl ribonucleosides were prepared by a convergent approach. Eldrup *et al.* synthesized 2′-*C*-*β*-ethyladenosine (**30**) from **26** in eight steps with very low overall yield (*Scheme 11*).[20] The glycosylating reagent, 1,3-di-*O*-acetyl-2,5-benzoyl-2-*C*-*β*-ethylribose, **29** was prepared from **26** in six steps with only 5% overall yield. Glycosylation of 6-chloropurine with **29** in the presence of trimethylsilyl triflate and DBU followed by aminolysis gave 2′-*C*-*β*-methyladenosine (**30**) in 16% yield.

The 2′-*C*-*β*-vinyl and ethynyl pyrimidine nucleosides (cytidine and uridine) were synthesized from 1,3,5-tri-*O*-benzoyl-2-ketoribose (**31**) by Harry-O'kuru *et al. via* the same approach for the synthesis of 2′-*C*-*β*-methylribonucleosides.[34] Reaction of the 2-ketoribose **31** with vinyl or trimethylsilylethynyl cerium chloride followed by benzoylation gave the 2-*C*-*β*-vinyl and 2-*C*-*β*-trimethylsilylethynylribose **32a** and **32b** in 84% and 75% yields, respectively. Glycosylation of persilylated bases with **32a** or **32b** in the presence of $SnCl_4$ gave perbenzoylated 2′-*C*-*β*-vinylnucleosides (**33a–b)** or 2′-*C*-*β*-ethynylnucleosides (**33c–d)** in 62–75% yield. Deprotection of **33a–d** with saturated ammonia in methanol gave 2′-*C*-*β*-vinyuridine (**34a**), 2′-*C*-*β*-vinycytidine (**34b**), 2′-*C*-*β*-ethynyluridine (**34c**), and 2′-*C*-*β*-ethynylcytidine (**34d**) in 83–91% yield (*Scheme 12*).



Scheme 12

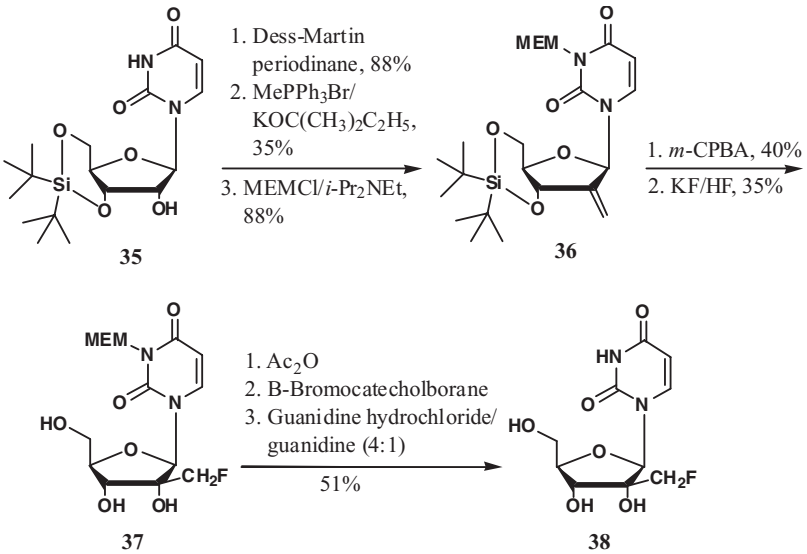
3. 2′-C-β-Fluoromethyl- and Alkoxymethylribonucleosides



R = CFH_2, CF_2H, CF_3, $ROCH_2$

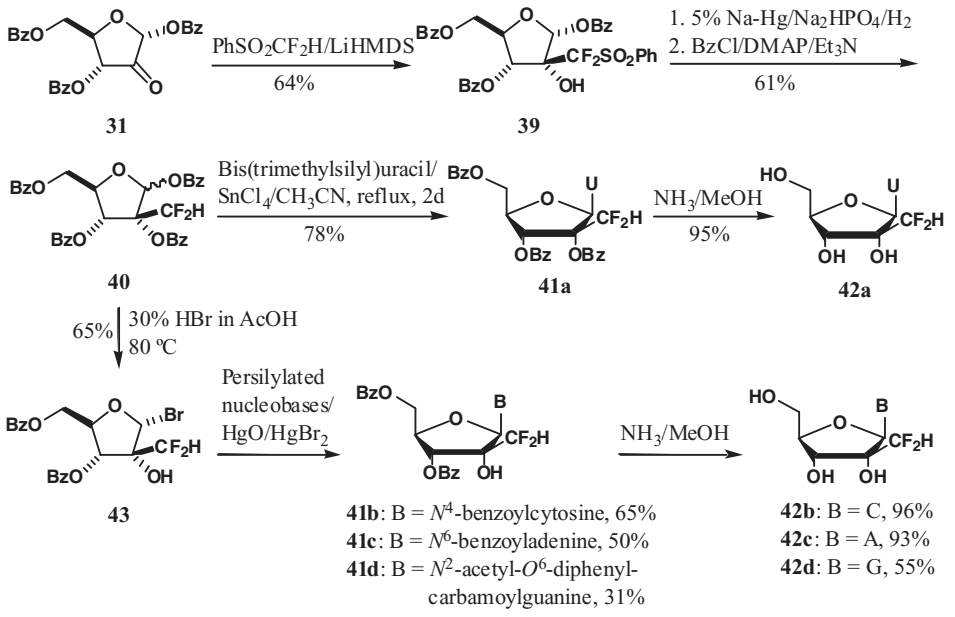
The 2′-*C*-β-fluoromethyl as well as 2′-*C*-β-alkoxymethyl nucleosides have been synthesized and used to study the mechanism of RNA cleavage reactions.[21] Dai *et al.* synthesized 2′-*C*-β-fluoromethyluridine (**38**) in eight steps from 3′,5′-*O*-di-*tert*-butylsilanediyluridine (**35**) *via* a linear approach.[39] The key steps include protection of the N^3 position of the uracil base of 2′-*C*-methyleneuridine (**36**) with MEM (methoxyethoxymethyl) chloride, conversion to the corresponding 2′-*C*-α-epoxide, and regioselective opening of the oxirane ring with potassium fluoride/hydrogen fluoride to give compound **37**. After subsequent acetylation, the MEM group was removed with *B*-bromocatecholborane and deacetylation under mild conditions to give 2′-C-β-fluoromethyluridine (**38**) (*Scheme 13*).

Ye *et al.* reported the synthesis of all four 2′-*C*-β-difluromethylribonucleosides (**42a–d**: A, C, G, U) starting from the 2-ketoribose **31** *via* the convergent approach (*Scheme 14*).[40] Addition of difluoromethyl phenyl sulfone to **31** followed by mild and efficient reductive desulfonation and benzoylation gave glycosylating agent **40** in good yield. Glycosylation of bis(trimethylsilyluracil) with **40** in the presence of $SnCl_4$ in refluxing acetonitrile for two days gave the uridine derivative **41a** in 78% yield. The glycosylating agent **39** was converted to a more reactive agent, 2-*C*-β-difluoromethyl ribofuranosyl bromide, **43** in 65% yield by reaction with 30% hydrogen bromide in acetic acid. The 1-bromo sugar **43** glycosylated persilylated cytosine, adenine and guanine to give the corresponding nucleoside derivatives



Scheme 13

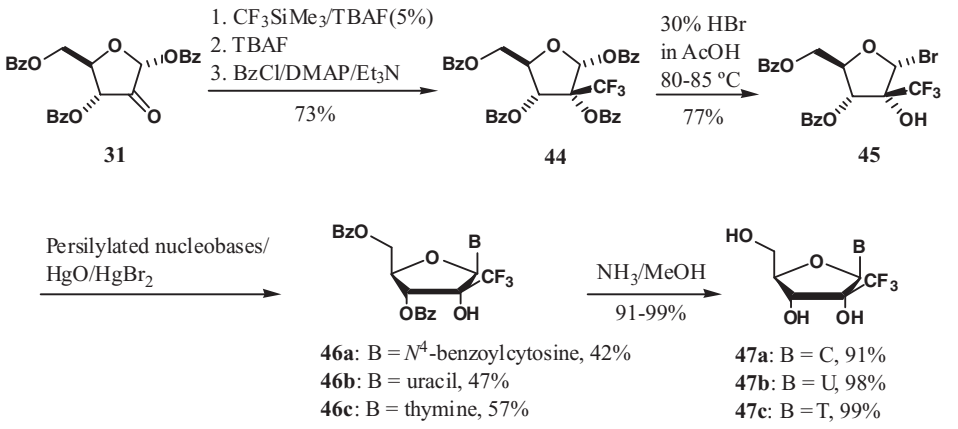
(**41b–d**) in 31–65% yield. Deprotection of **41a–d** with ammonia in methanol yielded 2′-*C*-*β*-difluromethyluridine (**42a**, 95% yield), 2′-*C*-*β*-difluromethylcytidine (**42b**, 96% yield), 2′-*C*-*β*-difluromethyladenosine (**42c**, 93% yield) and 2′-*C*-*β*-difluromethylguanosine (**42d**, 55% yield).



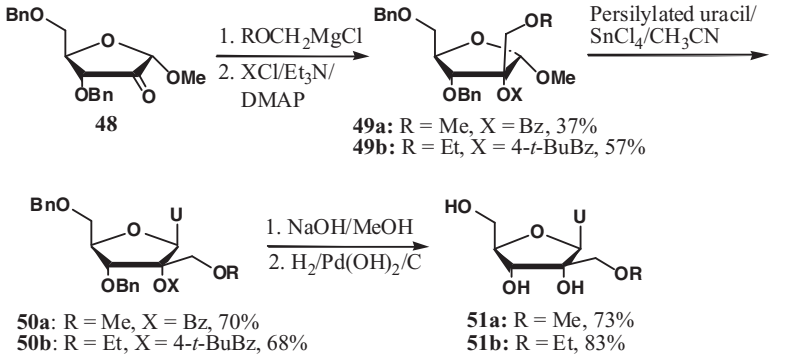
Scheme 14

The synthesis of 2′-*C*-*β*-trifluoromethyl pyrimidine ribonucleosides (**47a–c**: C, T, U) were accomplished by Li *et al.* (*Scheme 15*).[41] 1,2,3,5-Tetra-*O*-benzoyl-2-*C*-*β*-trifluoromethyl-*α*-D-ribofuranose (**44**) was prepared in 73% yield by the trifluoromethyl anion addition to the 2-ketoribose derivative **31** and converted to 3,5-di-*O*-benzoyl-2-*C*-*β*-trifluoromethyl-*α*-D-1-ribofuranosyl bromide (**45**) in 77% yield. The reaction of silylated pyrimidines with **45** in the presence of $HgO/HgBr_2$ afforded exclusively the *β*-anomers (**46a–c**) in 42–57% yield. Deprotection of **46a–c** with ammonia in methanol yielded the 2′-*C*-*β*-trifluoromethylcytidine (**47a**), 2′-*C*-*β*-trifluoromethyluridne (**47b**) and 2′-*C*-*β*-trifluoromethyl-5-methyluridine (**47c**) in 91–99% yield.

Recently Li *et al.* developed an efficent synthesis of methyl 3,5-di-*O*-benzyl-2-ketoribofuranoside (**48**) and applied it to the synthesis of 2′-alkoxymethyluridine (*Scheme 16*).[42] Reaction of **48** with *in situ* generated alkoxymethylmagnesium chloride followed by benzoyl protection with benzoyl chloride or 4-*tert*-butylbenzoyl chloride generated benzoic esters **49a** and **49b** in 37% and 57% yield, respectively. Glycosylation of persilylated uracil with **49a** and **49b** in the presence of $SnCl_4$ genarated 2′-alkoxymethyluridine derivatives **50a** and **50b** in about 70% yield. 4-*tert*-Butylbenzoyl group could be used to activate the glycosylation with a hindered sugar substrate such as 2′-ethoxymethylribose derivative. Debezoylation with sodium hydroxide and debenzylation with palladium catalyzed hydrogenation gave 2′-methoxymethyluridine **51a** and 2′-ethoxymethyluridine **51b** in 73% and 83% yields, respectively.

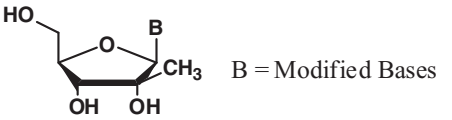


Scheme 15

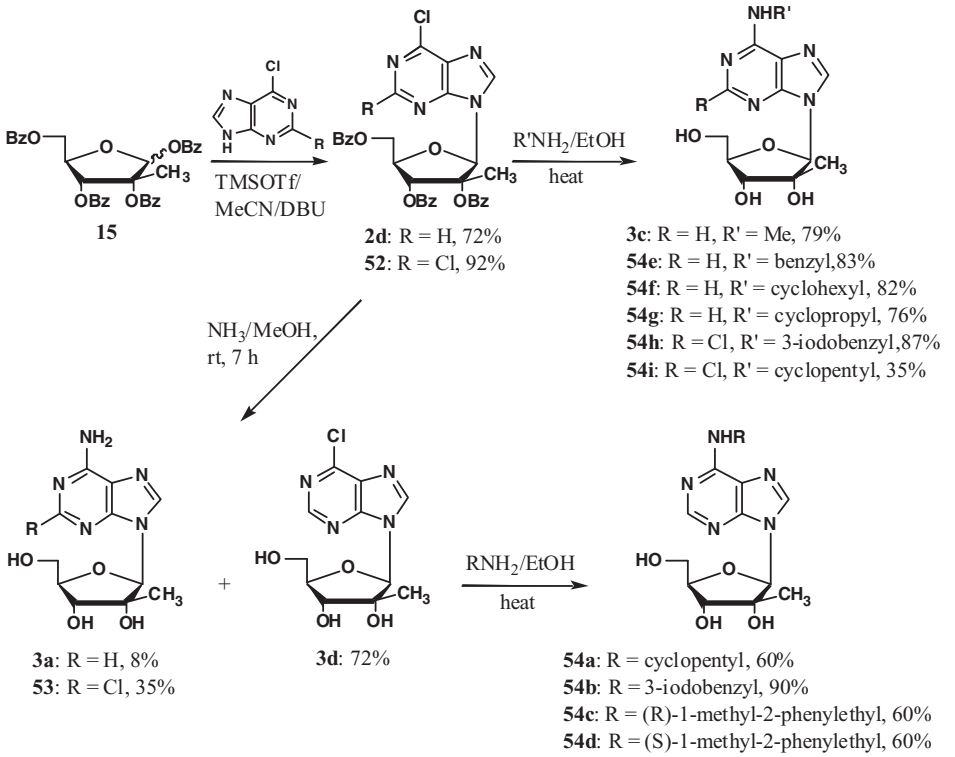


Scheme 16

4. 2′-C-β-Methyl Ribonucleosides with Modified Nucleobases



A series of 2′-*C*-*β*-methyladenosine analogues with potentially biological activities were synthesized by Franchetti *et al. via* aminolysis of 2′-*C*-*β*-methyl-6-chloropurine nucleosides (*Scheme 17*).[43–45] Glycosylation of perbenzoylated 2′-*C*-*β*-methylribofuranose (**15**) with 6-chloropurine or 2,6-dichloropurine in the presence of trimethylsilyl triflate and DBU gave 2′-*C*-*β*-methy-6-chloropurine nucleoside (**2d**) and 2′-*C*-*β*-methy-2,6-dichloropurine nucleoside (**52**) in 72% and 92% yields, respectively. Treatment of **2d** with ammonia in methanol at room temperature gave 6-chloro-9*H*-(2-*C*-methyl-*β*-D-ribofuranosyl)purine (**3d**, 72%) along with a small amount of 2′-*C*-*β*-methyladenosine (**3a**, 8%). The reaction of **52** with ammonia in methanol gave 2-chloro-2′-*C*-*β*-methyladenosine (**53**) in 35% yield. Aminolysis of **3d**, **2d** and **52** with various primary amines in ethanol gave N^4-substitituted-2′-*C*-*β*-methyladenosine derivatives (**54a–i**, **3c**) in 35–90% yield.[43–45]

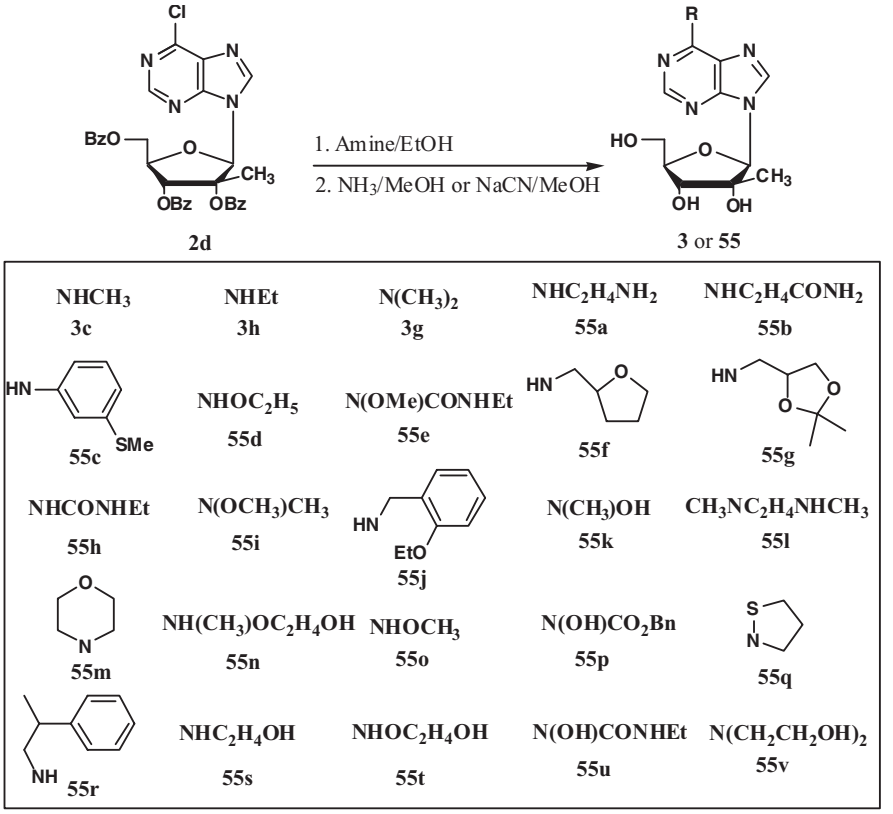


Scheme 17

By the aminolysis of **2d** with various primary amines or secondary amines, Ding *et al.* synthesized twenty-two new N^4-substituted 2′-*C*-β-methyladenosine nucleosides (**55a–v**) (*Scheme 18*).[46] However, in this paper the yields of **55a–v** from **2d** were not disclosed.

Treatment of **2d** with hydroxylamine followed by deprotection with NaCN/MeOH gave N^6-hydroxy-2-*C*-β-methyladenosine (**56a**).[46] Treatment of **2d** with hydroxylamine, followed by reaction with phenyl isocyanate, isopropyl isocyanate or ethyl isocyanate gave the N^6-carbamoyl-N^6-hydroxy-2-*C*-β-methyladenosine derivatives (**56b–d**). Treatment of **56a** with methyl orthoformate and propionyl chloride in pyridine in the presence of 1,2,4-triazole and TMSI yielded N^6-acyl-N^6-hydroxy-2-*C*-β-methyladenosine derivatives (**56e** and **56f**) (*Scheme 19*). Reaction of **2d** with zinc cyanide in the presence of $Pd(PPh_3)_4$ gave 6-cyanopurine nucleoside derivative (**57**)**.** Compound **57** was subsequently converted into **58a–c** by reactions with NH_2OH, NaCN/MeOH, and H_2S respectively. **2d** can also be converted into nucleosides: **59a–c** and **3j** by substitution and hydrolysis reactions with NaOMe, NaOEt, NaOH and NaSMe respectively. Suzuki coupling of **2d** with heteroaryl-boronic acids followed by aminolysis gave 2′-*C*-β-methylpurine nucleosides (**60a–c**).[46] However, the yields for all these transformations were also not disclosed.

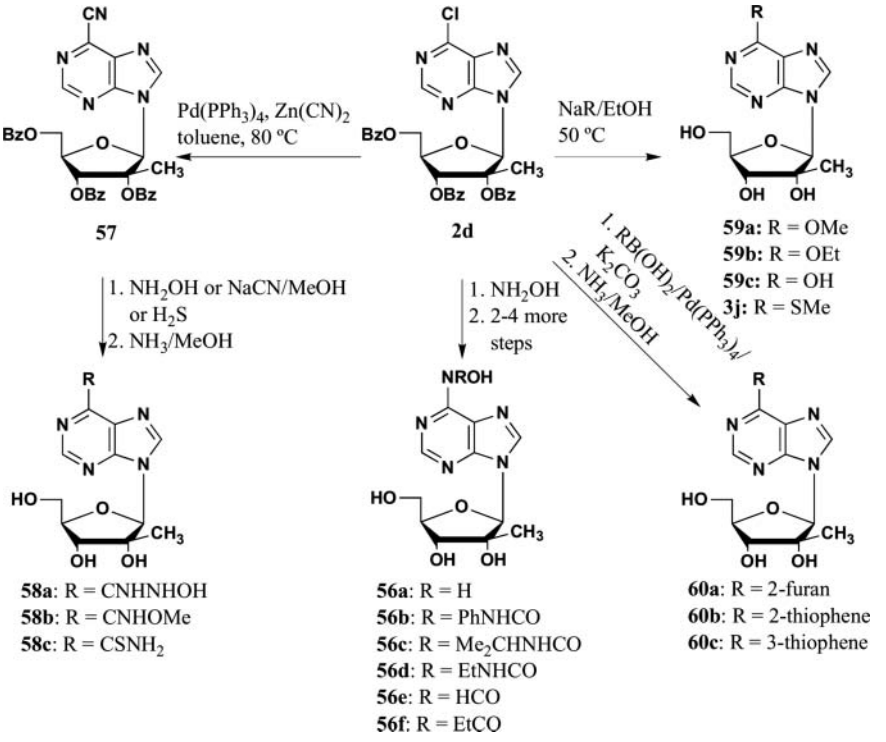
Hydrolysis of **3d** with sodium hydroxide yielded the 2′-*C*-β-methyl-β-D-ribofuranosyl hypoxanthine (**59c**) in 42% yield. Aminolysis of **19** with ammonium hydroxide gave 2,6-diaminopurine nucleoside (**3e**) in 58% yield. Hydrogen dehalogenation of **3d** and **19** in the



Scheme 18

presence of palladium on active carbon gave 2′-*C*-β-methylpurine nucleosides **3k** and **61** in 67% and 78% yields, respectively (*Scheme 20*).[20]

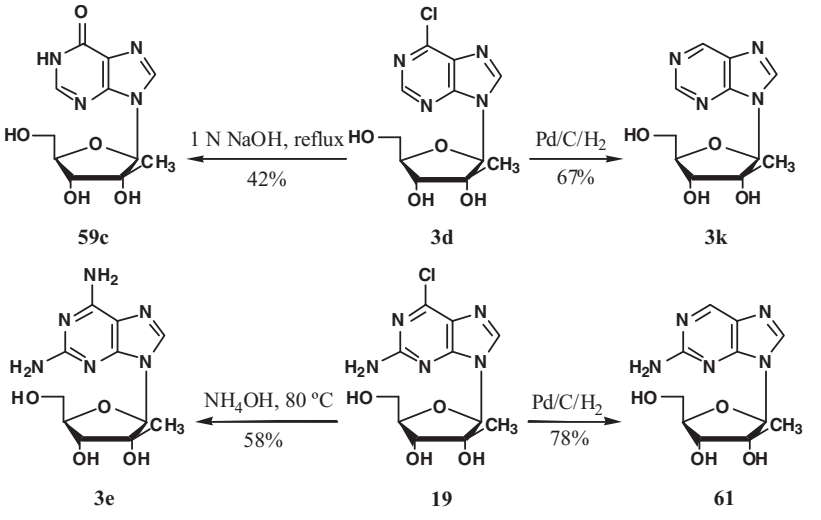
The 2′-*C*-β-methyl nucleoside with a modified nucleobase is generally prepared by the convergent approach, where the heterocyclic compound is glycosylated with the protected 2-*C*-β-methylribose. Eldrup *et al.*[47] reported that methyl 3,5-di-*O*-(dichlorobenzyl)-2-*C*-β-methylribofuranoside (**62**) could be converted to the corresponding more reactive ribofuranosyl bromide, which then reacted with the sodium or potassium salt of 7-deazapurines to give the glycosylation products (**63a–c)** in 40–66% yield (*Scheme 21*). Removal of the dichlorobenzyl group with boron trichloride yielded 7-deaza-6-chloro purine nucleosides (**64a–c**) in 66–84% yield. Treatment of **64a–c** with ammonia or ammonium hydroxide gave 7-deaza adenosine nucleosides (**65a–c**) in 56–69% yield. Chlorination (with *N*-chlorosuccinimide) or bromination (with *N*-bromosuccinimide) of **65a** gave 7-halogenated 7-deaza adenosine nucleosides **66a** and **66b** in 48% and 43% yields, respectively. Oxidation of the 7-methyl group of **65c** with hydrogen peroxide generated the carboxylic acid nucleoside derivative **66c** in 41% yield. 2-Fluorination by selective transformation of the more activated 2-amino group of **65b** at low temperature gave nucleoside **66d** in 30% yield. Direct hydrolysis or chloronation (with *N*-chlorosuccinimide) followed by



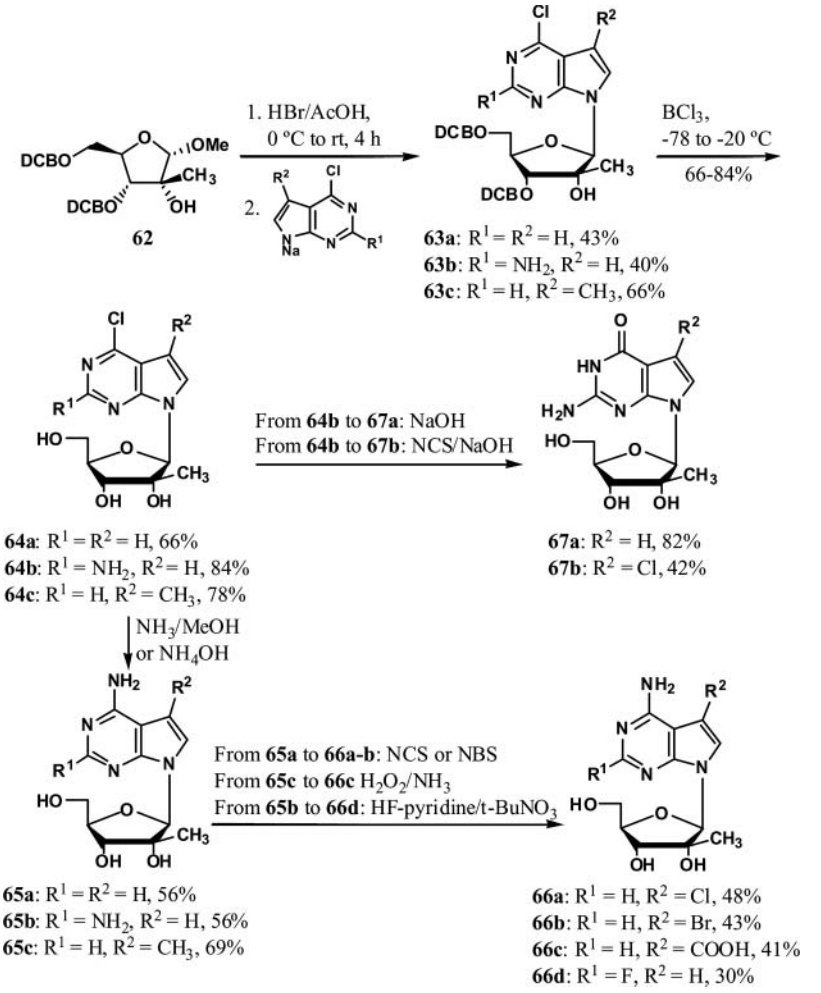
Scheme 19

hydrolysis of **64b** gave the 7-deaza-2′-*C*-*β*-methylguanosines **67a** and **67b** in 82% and 42% yields, respectively.

The 7-fluoro analogue of **66a** (7-chloro) and **66b** (7-bromo) was also synthesized by Eldrup *et al.* (*Scheme 22*).[47] Reaction of 2,3,5-tri-*O*-benzoyl-2-*C*-*β*-methylribose (**68**)[34] with



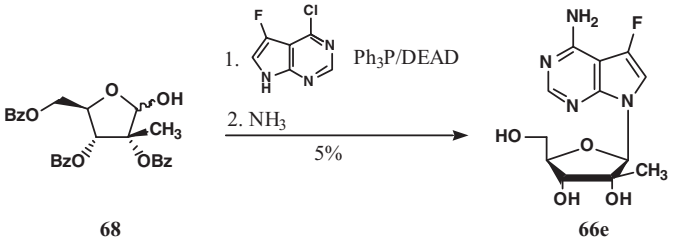
Scheme 20



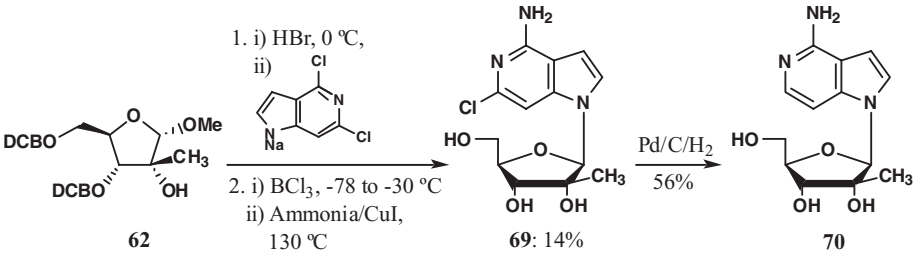
Scheme 21

4-chloro-5-fluoro-1*H*-pyrrolo[2,3-d]pyrimidine in the presence of triphenylphosphine and DEAD followed by deprotection with ammonia gave the desired 7-deaza-7-fluoroadenosine (**66e**) in low yield (only 5%).

3,7-Dideaza-2′-*C*-methyladenosine (**70**) was also synthesized from methyl 3,5-di-*O*-(dichlorobenzyl)-2-*C*-β-methylribofuranoside (**62**) (*Scheme 23*).[47] Compound **62** was first



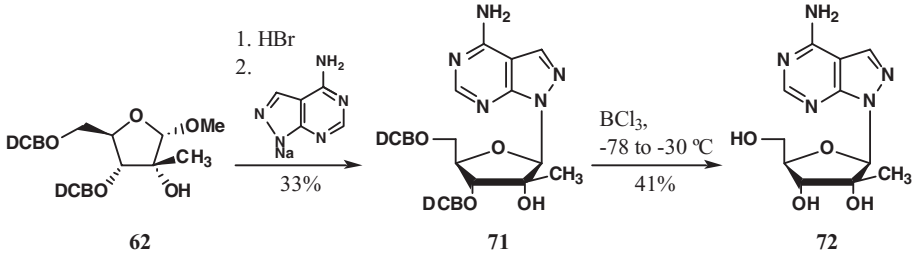
Scheme 22



Scheme 23

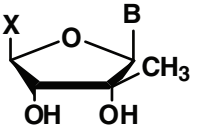
converted to a more reactive 1-bromo derivative and then reacted with the sodium salt of dichloro-1*H*-pyrrolo[3,2-c]pyridine to give the glycosylation product in 37% yield. Subsequently debenzylation and amination gave 3,7-deaza-2-chloro-2′-*C*-*β*-methyladenosine (**69**) in 14% overall yield. Palladium catalyzed dehalogenation of **69** gave 3,7-dideaza-2′-*C*-methyladenosine (**70**) in 56% yield.

Similarly, the reaction of the 1-bromo derivative of compound **62** with the sodium salt of 4-amino-1*H*-pyrazolo[3,4-d]pyrimidine afforded intermediate **71** in 33% yield. Debenzylation of **71** with boron trichloride at low temperature gave 8-aza-7-deaza-2′-C-methyladenosine (**72**) in 41% yield (*Scheme 24*).

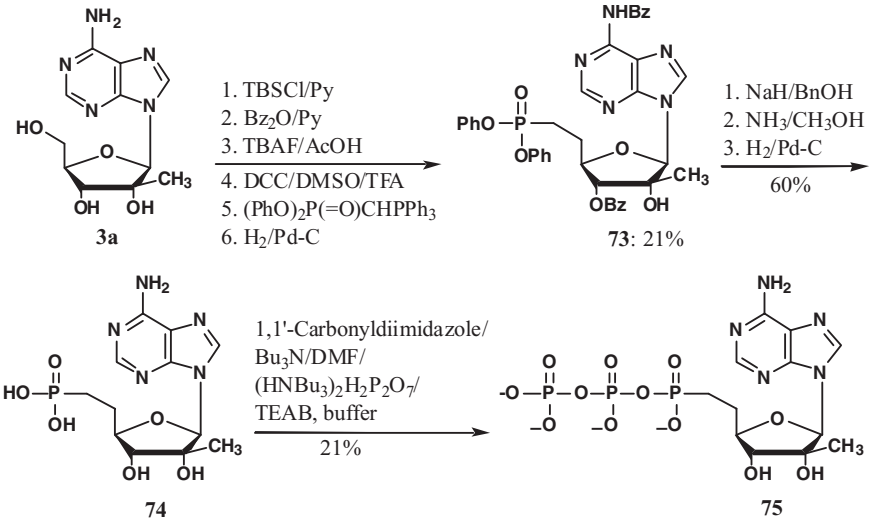


Scheme 24

*5. 5′-Modified-2′-*C*-β-Methyl Ribonucleosides*



Koh *et al.* prepared the triphosphonate (**75**) of 5′-modified 2′-*C*-*β*-methyladenosine from 2′-*C*-*β*-methyladenosine (**3a**) to mimic naturally occurring adenosine triphosphonate (*Scheme 25*).[48] The 3′-hydroxyl and 6-amino groups of nucleoside **3a** were protected with benzoyl groups and the 5′-hydroxyl group was oxidized to 5′-aldehyde, which was then reacted with a *α*-phosphonate substituted phosphorus ylide to yield an *α*,*β*-unsaturated

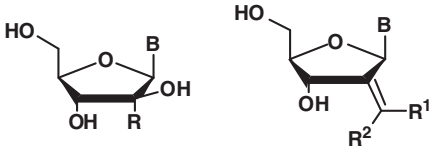


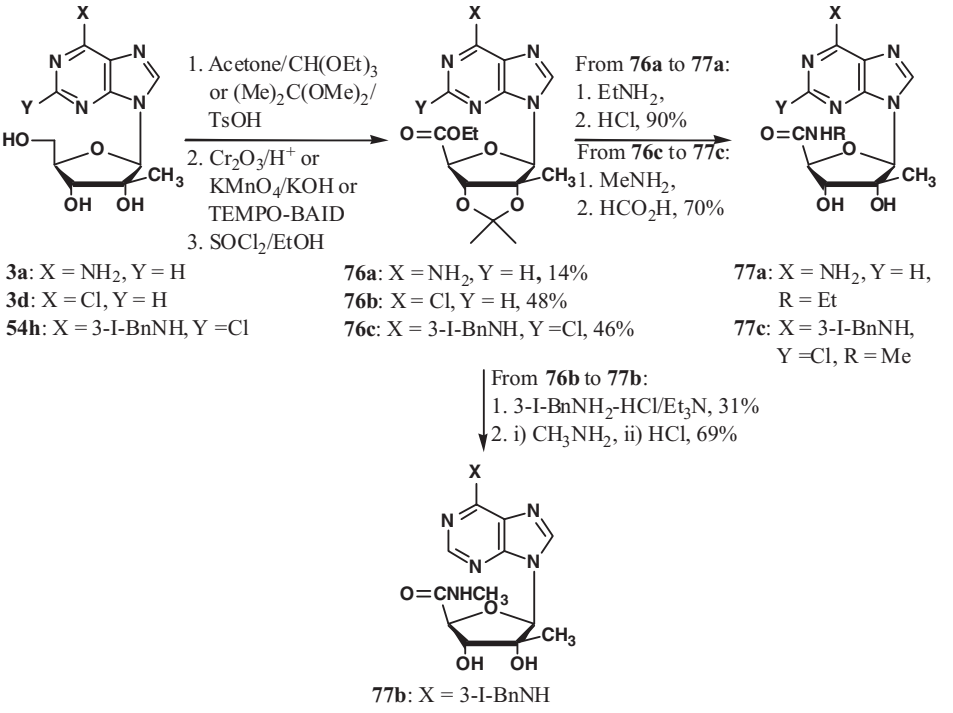
Scheme 25

phosphate nucleoside derivative. Hydrogenation converted the α,β-unsaturated phosphonate ester to saturated 5′-phosphonate ester nucleoside derivative **73**. Compound **73** was then converted to the 5′-monophosphonate (**74**) in 60% yield. The 5′-monophosphonate **74** was further converted to 5′-triphosphonate (**75**) in 21% yield.

Grifantini *et al.* synthesized 5′-carboxylic amide of 2′-*C*-β-methyladenosine derivatives **77a–c** from the corresponding 2′-*C*-β-methyladosine derivatives **3a**, **3d** and **54h** (*Scheme 26*).[43,45] The synthetic route includes steps of protection of the 2′,3′ *cis*-diol with isopropylidene, oxidation of the 5′-hydroxyl group to the corresponding carboxylic acid and transformation of the 5-carboxylic group into esters **76a–c** in 14–48% yield. Aminolysis of the 5′-ethyl carboxylate ester of **76a** and **76c** with methyl or ethylamine followed by removal of isopropylidene group under acidic condition generated the 5′-carboxylic amide nucleosides **77a** and **77c** in 90% and 70% yields, respectively. Selective substitution of the 6-chloro atom of **76b** with 3-iodobenzylamine and subsequent aminolysis of the 5′-ethyl carboxylate ester with methylamine followed by removal of isopropylidene group under acidic condition gave **77b** in three steps with 21% overall yield.

II. 2′-*C*-Branched Arabinonucleosides and 2′-*C*-Methylene-2′-Deoxynucleosides





3a: X = NH_2, Y = H
3d: X = Cl, Y = H
54h: X = 3-I-BnNH, Y =Cl

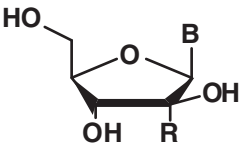
76a: X = NH_2, Y = H, 14%
76b: X = Cl, Y = H, 48%
76c: X = 3-I-BnNH, Y =Cl, 46%

77a: X = NH_2, Y = H, R = Et
77c: X = 3-I-BnNH, Y =Cl, R = Me

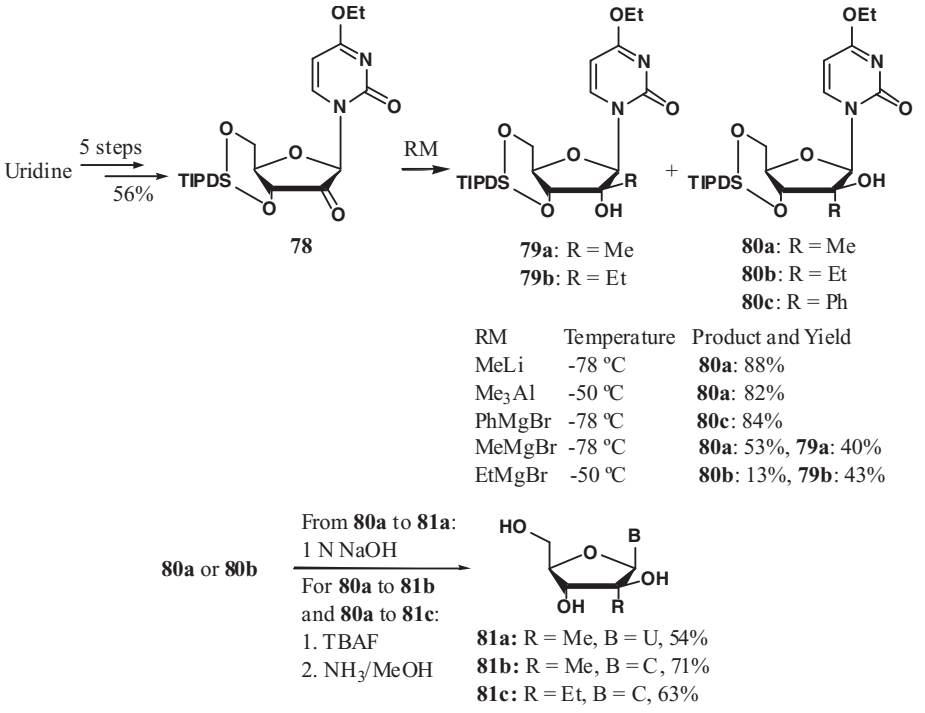
77b: X = 3-I-BnNH

Scheme 26

1. 2′-C-Branched Arabinonucleosides



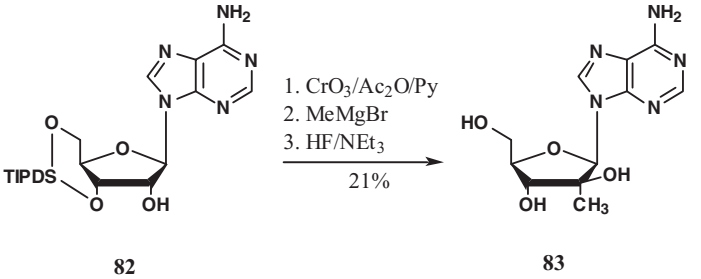
The 2′-*C*-branched arabinonucleosides are important nucleoside analogues which have served as useful precursors to 2′-*C*-β-branched 2′-deoxynucleosides. (The synthesis of 2′-*C*-β-branched 2′-deoxynucleosides *via* deoxygenation of 2′-*C*-branched arabinonucleosides is described in *Section III*.) The 2′-*C*-branched arabinonucleosides are generally prepared stereoselectively by the addition reaction of organometallic reagents to the 2′-ketonucleoside derivatives. For example, Matsuda *et al.* prepared 2′-*C*-α-methylarabinouridine (**81a**), 2′-*C*-α-methylarabinocytidine (**81b**) and 2′-*C*-α-ethylarabinocytidine (**81c**) starting from uridine (*Scheme 27*).[8] To facilitate the addition reaction of organometallic reagents to 2′-ketonucleoside, uridine was converted into 2′-ketonucleoside derivative (**78**) in five steps with 56% overall yield. Addition of methyllithium, trimethylaluminum, or phenylmagnesium bromide to **78** yielded the corresponding arabinonucleoside derivatives **80a** and **80c** exclusively. However, addition of methylmagnesium bromide or ethylmagnesium bromide to **78** yielded the 2′-branched arabinonucleoside derivatives **80a** and **80b** along with a larger portion of 2′-branched ribonucleoside



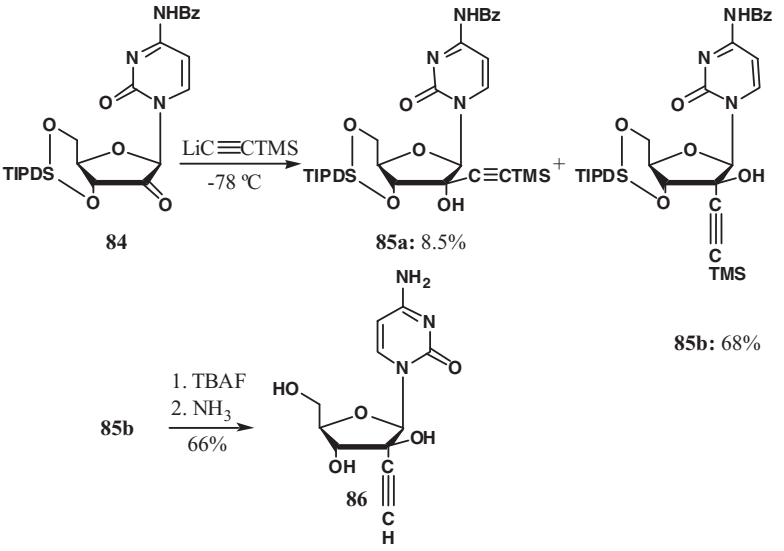
Scheme 27

derivatives **79a** and **79b**. The β-addition of MeMgBr and EtMgBr to **78** could be explained by chelation of the metal between 2- and 2′-carbonyls at the base and sugar moieties, which delivered the methyl carbanion from the sterically more hindered β-face. Hydrolysis of **80a** with aqueous NaOH (at room temperature for 23 h then at 60°C for 90 min) removed the TIPDS group and yielded the 2′-*C*-methylarabinouridine (**81a**) in 54% yield. Desilylation of **80a** and **80b** with TBAF followed by amination with NH_3/MeOH at 100°C gave 2′-*C*-α-methylarabinocytidine (**81b**) and 2′-*C*-α-ethylarabinocytidine (**81c**) in 71% and 63% yields, respectively.

Similarly, Eldrup *et al.* prepared 2′-*C*-methylarabinoadenosine (**83**) from 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine (**82**) in three steps (oxidation, addition, and desilylation) with 21% overall yield (*Scheme 28*).[20]



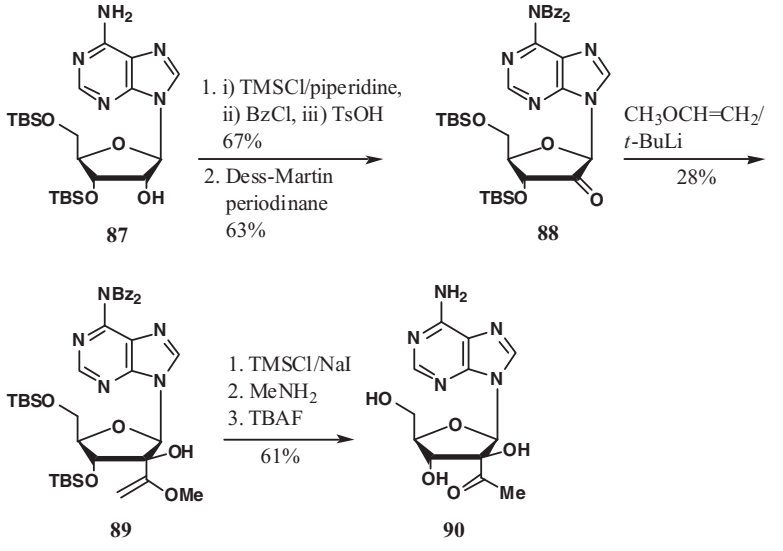
Scheme 28



Scheme 29

Hattori *et al.* synthesized 2′-*C*-ethynylarabinocytidine (**86**) as a major product (three steps, 45% overall yield) by the addition of trimethylsilylethynyllithium to 4-benzoyl-2′-ketocytidine derivative (**84**). The addition reaction gave a 2′-arabinocytidine derivative **85b** in 68% yield along with a 2′-*C*-*β*-alkynylcytidine derivative **85a** in 8.5% yield. Desilylation of **85b** followed by removal of the benzoyl group gave 2′-*C*-ethynylarabinocytidine **86** in 66% yield (*Scheme 29*).[49]

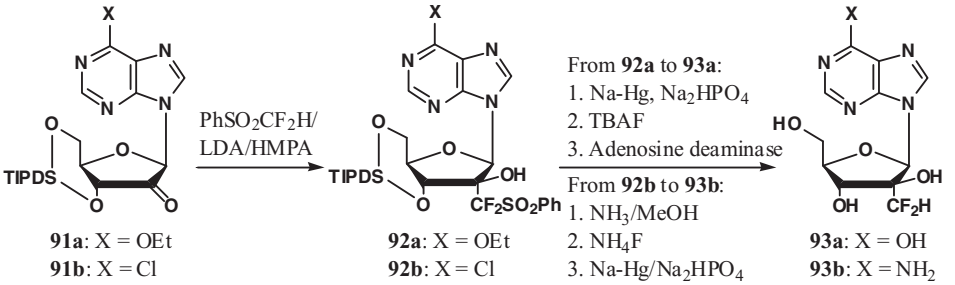
2′-Acetylarabinoadenosine (**90**) was synthesized by Chatgilialoglu *et al. via* a linear approach (*Scheme 30*).[50] Starting from 3′,5′-di-*O*-TBS-adenosine (**87**), the amino group



Scheme 30

was selectively protected with two benzoyl groups in 67% yield. Oxidation with Dess-Martin periodinane gave 2′-ketoadenosine derivative **88** in 63% yield. Addition of the *in situ* generated α-methoxyvinyllithium (methyl vinyl ether/*tert*-butyllithium) to **88** yielded the corresponding 2′-branched arabinoadenosine derivative **89** in 28% yield. Hydrolysis of the vinyl ether and deprotection (removal of benzoyl group and desilylation) gave the 2′-acetylarabinoadenosine (**90**) in 61% yield.

Dunkel *et al.* reported the synthesis of 2′-*C*-difluoromethylarabinonucleosides (**93a**: an inosine analogue and **93b**: an adenosine analogue) from inosine *via* nine chemical steps (*Scheme 31*).[51] Compounds **91a** and **91b** were prepared from inosine (five steps) and alkylated by phenyldifluoromethylsulfone-LDA to give arabinonuceloside derivatives **92a** and **92b**. Compound **92a** was then converted to **93a** by desulfonation with Na-Hg, desilyation with TBAF, and hydrolysis with adenosine deaminase. Compound **92b** was converted to **93b** *via* a modified reaction sequence (amination with NH_3/MeOH, desilylation with TBAF, and then desulfonation with Na-Hg). However, the yields were not reported.



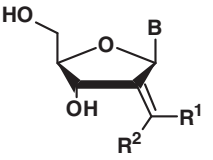
91a: X = OEt
91b: X = Cl

92a: X = OEt
92b: X = Cl

93a: X = OH
93b: X = NH_2

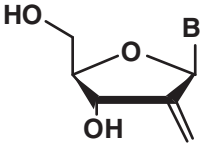
Scheme 31

*2. 2′-*C*-Methylene-2′-deoxynucleosides and Derivatives*

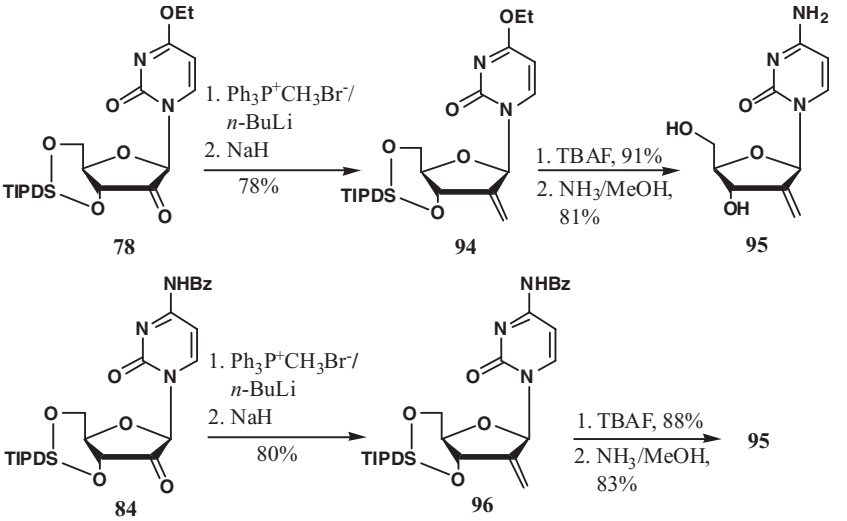


2′-*C*-Methylene-2′-deoxyribonucleoside derivatives have shown potential antitumor activity[52] and also have served as useful precursors to other 2′-branched nucleosides as described in *Section III*.

*a) 2′-*C*-Methylene-2′-deoxynucleosides*



Matasuda *et al.*[3] originally prepared 2′-*C*-methylenecytidine (**95**) from uridine in eight steps *via* Wittig reaction of 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2′-keto-4-*O*-ethyluridine (**78**) with methylenetriphenylphosphorane. The olefin yield increased from 41% to 78% by using sodium hydride as an additional base. Desilylation of **94** followed by amination with ammonia gave 2′-*C*-methylene-2′-cytidine **95** with an overall yield of 73%. However, this approach is relatively long because the synthesis of **78** from uridine required five additional chemical steps. Subsequently, they prepared **95** directly *via* Wittig reaction of 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2′-keto-N^4-benzoylcytidine (**84**) with methylenetriphenylphosphorane (*Scheme 32*).[3] **84** could be prepared from N^4-benzoylcytidine in two steps and reacted with methylenetriphenylphosphorane to give the 2′-methylenecytidine derivative **96** in 80% yield. Deprotection of **96** with TBAF and ammonia in methanol gave 2′-*C*-methylenecytidine (**95**) in 73% combined yield.

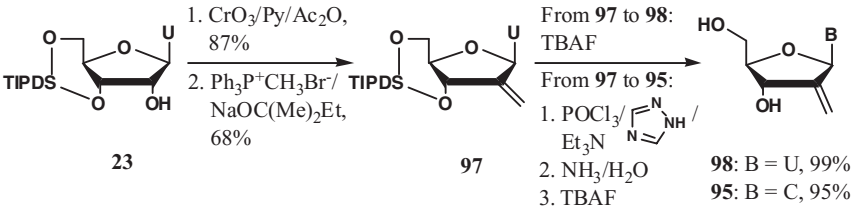


Scheme 32

An alternative approach to obtain **95** from uridine was developed by Samano *et al. via* Wittig reaction of 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2′-ketouridine or 3′,5′-bis-*O*-*tert*-butyldimethylsilyl-2′-ketouridine with $Ph_3P^+CH_3Br^-$/$NaOC(Me)_2Et$.[53] The 2′-methyleneuridine derivative (**97**) was obtained from **23** in two steps with 59% yield. Compound **97** were desilylated to give 2′-*C*-methyleneuridine (**98**) directly (99% yield) or transformed into the corresponding cytidine derivative (**95**) (95% yield) (*Scheme 33*).

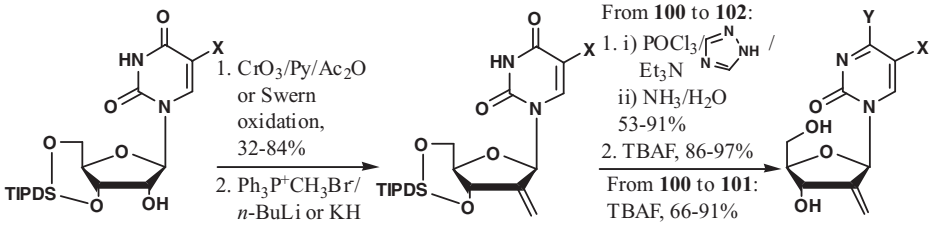
Via the same synthetic approach as shown in *Scheme 33*, Matsuda *et al.*[3] and Lin *et al.*[54] synthesized a series of 5-substitued (F, Cl, Br, I, methyl, ethyl, ethynyl) 2′-methyleneuridines (**101a–g**) and cytidines (**102a–g**) starting from the corresponding 5-substituted 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine derivatives (**99a–g**) (*Scheme 34*).

Czernecki *et al.* improved the yield of 2′-methyleneuridine derivative (**97**) to 70% overall yield from **23** (compared to 59% obtained from *Scheme 33*) in two steps by using PDC/AcOH as the oxidizing agent and a stronger base *s*-BuLi in the Wittig reaction.



23 **97**

Scheme 33



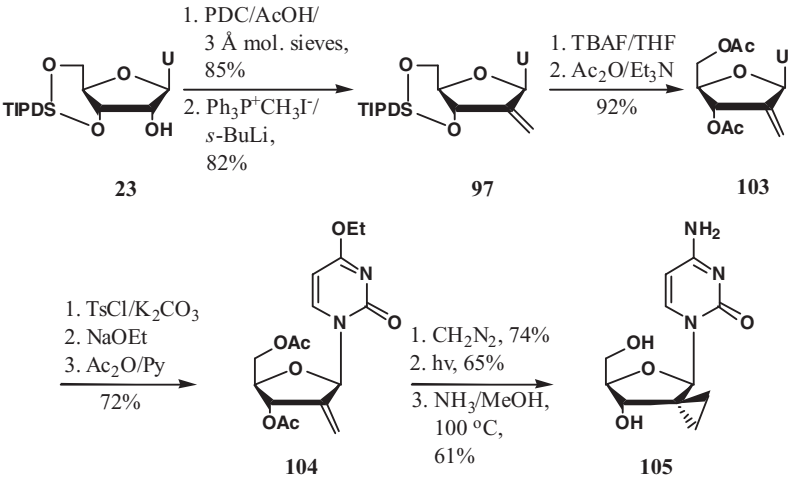
99a-g **100a-g** **101a-g**: Y = OH
102a-g: Y = NH_2

a: X = F, **b**: X = Cl, **c**: X = Br, **d**: X = I, **e**: X = Me, **f**: X = Et, **g**: X = ethynyl

Scheme 34

Compound **97** was then converted into 2′-deoxy-2′-spirocyclopropyl cytidine (**105**) in eight steps with 19% overall yield (*Scheme 35*).[55]

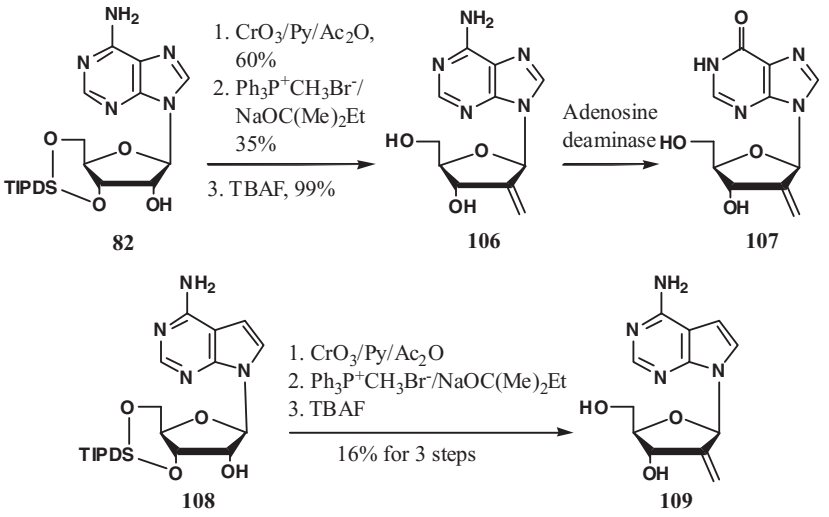
The 2′-methylenepurine nucleosides were also prepared. Samano et al prepared 2′-methyleneadenosine (**106**) *via* the Wittig reaction of 3′,5′-*O*-TIPDS-2′-ketoadenosine with methylenetriphenylphosphorane (*Scheme 36*).[56] The 2′-methyleneinosine (**107**) was also



23 **97** **103**

104 **105**

Scheme 35



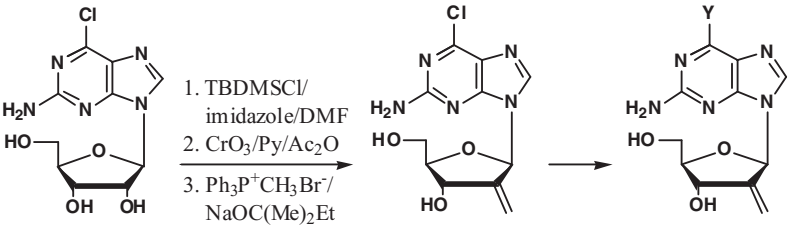
82 **106** **107**

108 **109**

Scheme 36

obtained quantitatively by the treatment of **106** with adenosine deaminase. Robins *et al.* prepared 2′-deoxy-2′-methylenetubercidin (**109**) from 3′,5′-*O*-TIPDS-tubercidin (**108**) in three steps *via* oxidation to 2′-ketonucleoside, Wittig reaction to 2′-methylenenucleoside, and desilylation to give **109** in 16% overall yield.[57]

Robins *et al.* also prepared 2-amino-6-chloro-9-(2-deoxy-2-methylene-β-D-erythro-pentofuranosyl)purine (**111**) in four steps from 2-amino-6-chloro-9-(β-D-ribofuranosyl)purine (**110**) with 13% overall yield (*Scheme 37*).[57] The 6-chloro group of 2′-methylene purine nucleoside derivative (**110**) was then substituted by NH_2 with NH_3/MeOH, OH with adenosine deaminase, NMe_2 with $NHMe_2$, OMe with NaOMe, SH with NaSH, and SMe with NaSMe to give the 2′-methylene purine nucleoside derivatives **112a–f** in 58–91% yield.



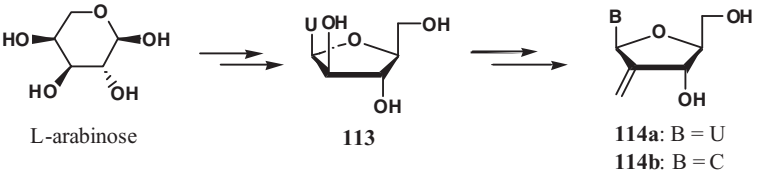
110 **111**

13% overall yield

112a: Y = NH_2 , 87%, (NH_3/MeOH)
112b: Y = OH, 73%, (Adenosine deaminase)
112c: Y = NMe_2, 91%, ($NHMe_2$)
112d: Y = OMe, 80%, (NaOMe)
112e: Y = SH, 82%, (H_2S/NaOMe)
112f: Y = SMe, 58%, (NaSMe)

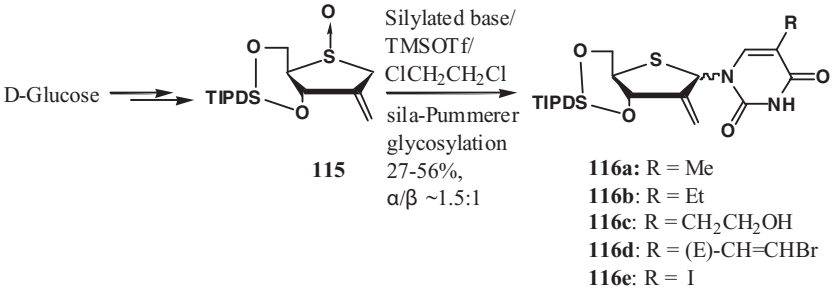
Scheme 37

The enantiomers of 2′-methyleneuridine (**98**) and 2′-methylenecytidine (**95**) were synthesized from L-arabinose by Lin *et al. via* a key intermediate **113**.[58] The enantiomers: **114a** and **114b** were obtained from **113** by protection with $TIPDSCl_2$, oxidation with chromium oxide, Wittig reaction with methylenetriphosphorane, and desilyalation with TBAF as for the synthesis of 2′-methyleneuridine (**98**) and 2′-methylenecytidine (**95**) (*Scheme 38*).[58]



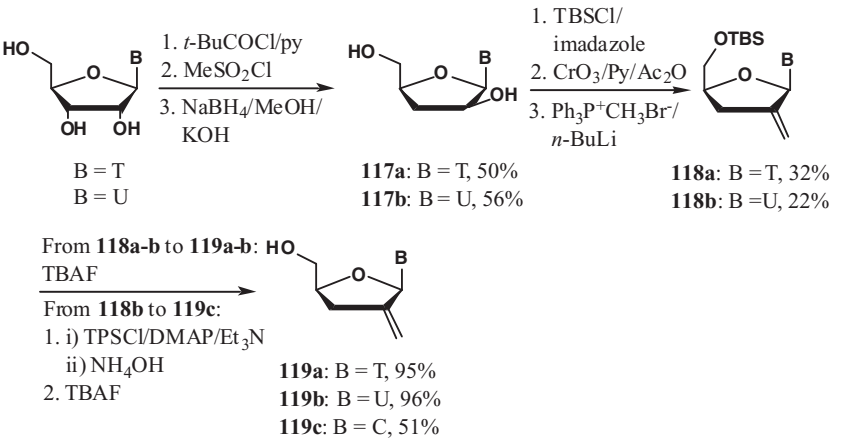
Scheme 38

Satoh *et al.* reported that 4′-thionucleosides could be prepared starting from D-glucose (*Scheme 39*).[59] The sila-Pummerer glycosylation reaction of **115** with persilylated thymine, 5-ethyluracil, and 5-hydroxyethyluracil gave the corresponding 4′-thionucleoside derivatives **116a–c** respectively ($\alpha/\beta = 1.5$–1.7). In contrast, the same reaction using uracils with electron-withdrawing substituents at the 5-position, such as 5-(*E*)-bromovinyl and 5-iodo, gave **116d** and **116e** in low yields with very low β-selectivity. It was reported that in the presence of triethylamine both yield and β-selectivity were improved in the glycosylation of 5-bromovinyl- and 5-iodouracils. Desilylation of **116a–c** gave the corresponding 4′-thionucleosides.



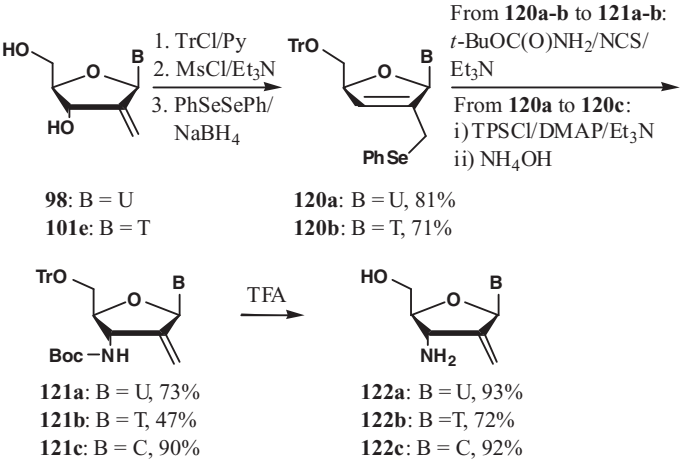
Scheme 39

The 3′-deoxy-2′-methylenepyrimidine nucleosides **119a–c** were prepared by Matsuda *et al.* starting from uridine and thymidine (*Scheme 40*).[60] 3′-Deoxy-β-D-*threo*-pentofuranosyl nucleosides **117a–b** could be prepared from the corresponding ribonucleosides by two one-pot reactions including the deoxygenative [1,2]-hydride shift of the 3′-*O*-methanesulfonates in 50–56% yields.[61] Compounds **117a** and **117b** were converted to the corresponding 5′-*O*-TBS-3′-deoxy-2′-methylenethymidine and uridine (**118a–b**) in three steps with 32% and 22% yields, respectively. Desilylation of **118a–b** with TBAF gave the free nucleosides **119a–b** in good yields. 5′-*O*-TBS-3′-deoxy-2′-methyleneuridine (**118b**) was also converted to the cytidine derivative by reaction with triisopropylbenzenesulfonyl chloride (TPSCl) followed by aminolysis with NH_4OH and desilylation with TBAF to give **119c** in 51% yield.



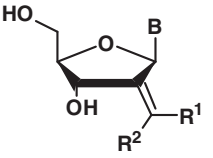
Scheme 40

2′-Methyleneuridine (**98**) and 2′-methylenethymidine (**101e**) were used as starting materials to prepare 3′-amino-2′-methylene pyrimidine nucleosides **122a–c** (*Scheme 41*).[62] The 2′-methylenenucleoside derivatives were first converted into 2′,3′-didehydro-2′-phenylselenomethylnucleosides **120a–b** in three steps with 71–81% yield. Treatment of **120a–b** with NCS in the presence of *tert*-butylcarbamate and triethylamine generated the corresponding 3′-*tert*-butoxycarbonylamino-2′-methylidene derivative **121a–b** in 73% and 47% yields, respevtively. The uridine derivative **121a** was converted to the cytidine derivative **121c** in 90% yield by reaction with TPSCl/DMAP/Et_3N followed by aminolysis with NH_4OH. Trifluoroacetic acid (TFA) treatment of **121a–c** removed the trityl and Boc groups to afford the 3′-amino-2′-methylene pyrimidine nucleosides **122a–c** in 72–93% yield.

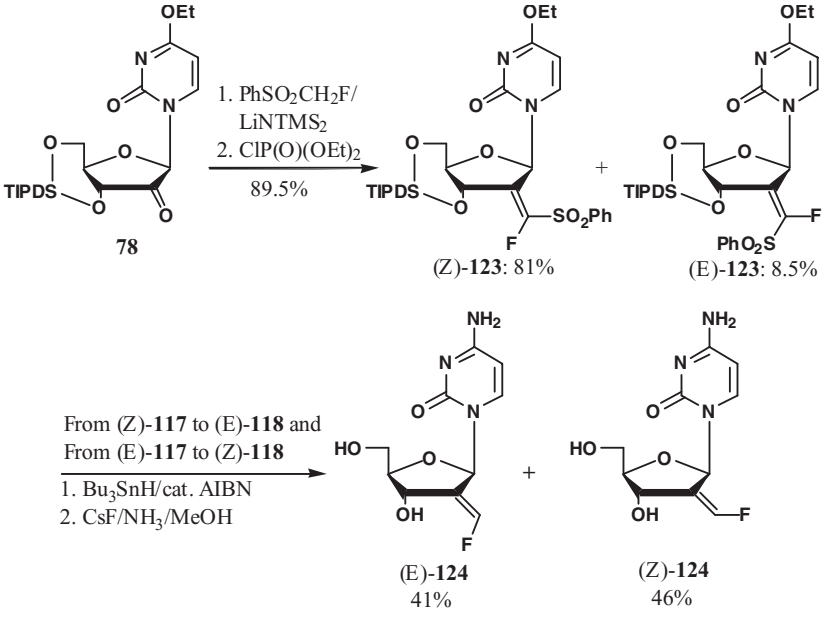


Scheme 41

b) 2′-C-(Substituted Methylene)-2′-deoxynucleosides



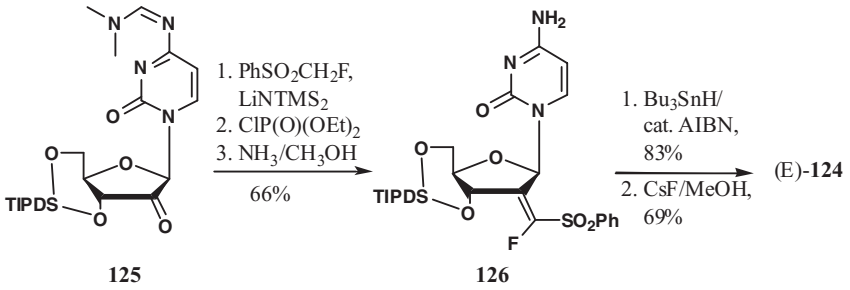
Since 2′-*C*-methylene-2′-deoxynucleosides have been shown to have biological activity as enzyme inhibitors, the syntheses of 2′-*C*-(substituted methylene)-2′-deoxynucleosides were also developed. For example, McCarthy *et al.* prepared both 2′-(*E*)- and (*Z*)-fluoromethylenecytidine **124** starting from 4-ethoxyl-2′-ketonucleoside derivative (**78**) (*Scheme 42*).[63,64] Using the Honer-Wittig reaction, **78** was converted to a mixture of readily separable fluorovinyl sulfone (Z)-**123** (81% yield) and (*E*)-**123** (8.5% yield). Reaction of the fluorovinyl sulfones [(*Z*)-**123** and (*E*)-**123**] with tributyltin hydride gave fluorovinylstannanes stereoselectively. Treatment of the fluorovinylstannanes with cesium fluoride and ammonia in methanol gave (*E*)-**124** and (*Z*)-**124** in 41% and 46% yields, respectively.



Scheme 42

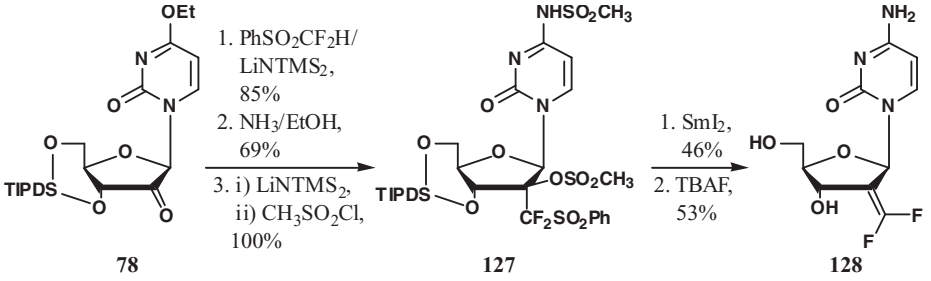
An improved synthesis of (*E*)-**124** was reported utilizing cytidine as starting material and incorporates stereospecifically to fluoro olefins as in the original process.[65] The 2′-ketocytidine derivative **125** could be prepared from cytidine in three steps in 77% yield. The new five-step route starting from 2′-ketocytidine derivative **125** gave an overall yield of 38% (*Scheme 43*).[65]

The 2′-*C*-difluoromethylenecytidine (**128**) was also prepared from 4-ethoxy-2′-ketonucleoside (**78**).[66] Addition of the difluoromethylphenyl sulfone anion to ketone **78** followed by amination and bismesitylation gave bismesitylated compound **127** in good yield. Reductive elimination of **127** with four equivalents of SmI_2-THF required heating at



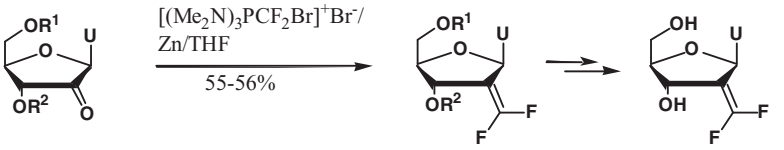
Scheme 43

55°C to complete the reaction and gave the olefin in 46% yield. Removal of the (TIPDS) group from olefin was accomplished using TBAF (53% yield), completing the synthesis of **128** (*Scheme 44*).



Scheme 44

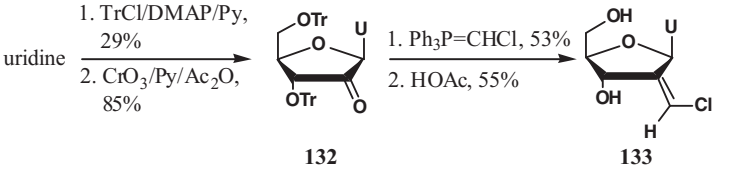
The 2′-difluoromethyleneuridine (**131**) and its phosphoramidite were prepared by Serafinowski *et al.* from 2′-ketouridine derivative **129a–b**.[67] The one pot reaction of **129a,b** with bromodifluoromethyl[tris(dimethylamino)phosphonium bromide and zinc gave the corresponding 2′-difluoromethylene nucleosides **130a-b** in 56% and 55% yields, respectively. Deprotection and phosphitylation gave the difluoromethylene uridine and corresponding phosphoramidite (*Scheme 45*).



Scheme 45

The Wittig reaction of 2′-keto-3′,5′-di-*O*-trityluridine (**132**) with chloromethylenetriphenylphosphorane followed by detritylation with acetic acid gave (*Z*)-chloromethyleneuridine **133** in 29% yield (*Scheme 46*).[68] The 2′-keto-3′,5′-di-*O*-

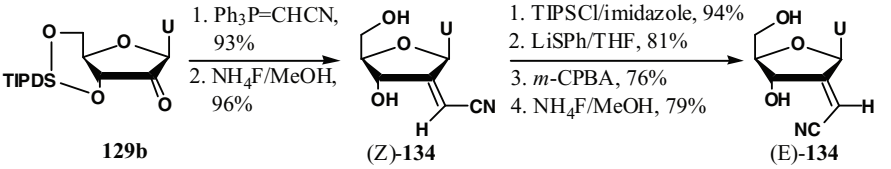
trityluridine (**132**) could be prepared from uridine in two steps (3′,5′-di-*O*-tritylation followed by oxidation) with 25% overall yield.



132 **133**

Scheme 46

The Wittig reaction of 2′-ketouridine (**129b**) with $Ph_3P = CHCN$ afforded the (*Z*)-2′-cyanomethylene derivative exclusively in 93% yield (*Scheme 47*). Removal of the TIPDS group with ammonium fluoride gave (*Z*)-2′-cyanomethyleneuridine (*Z*)-**134** in 96% yield. (*Z*)-**134** could be converted to the (*E*)-isomer in four steps with good yield and excellent selectivity. To accomplish the stereoisomerization, a large TIPS (triisopropylsilyl) group was first introduced at the 5′-position, enabling stereoselective benzenethiolate addition. Subsequent oxidative syn-elimination followed by removal of the TIPS group with fluoride anion gave (*E*)-**134** in 79% yield (*Scheme 47*).[69]



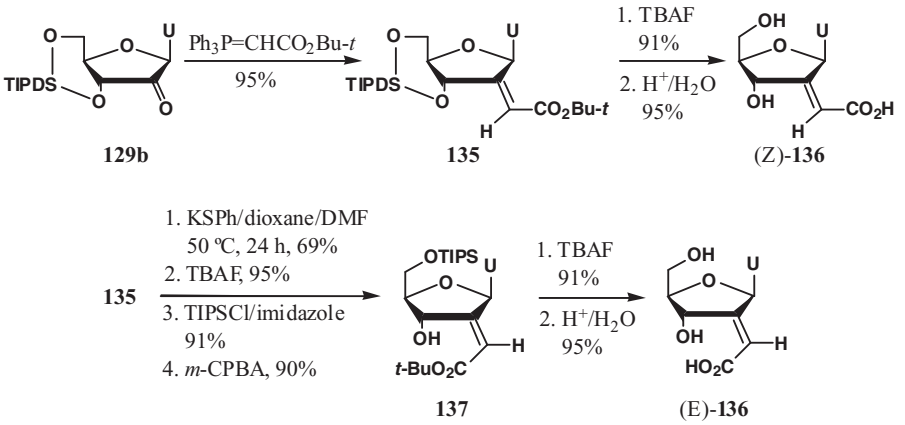
129b (Z)-**134** (E)-**134**

Scheme 47

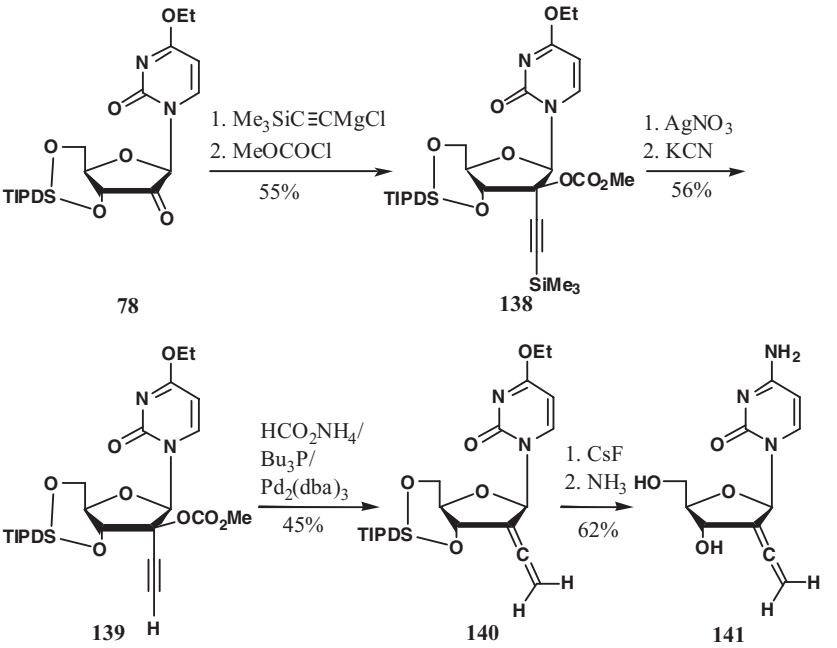
Both 2′-(Z/E)-(carboxymethylene)-2′-deoxyuridines (**136**) were synthesized using a similar synthetic approach as for the synthesis of (E/Z)-**134** (*Scheme 48*).[70] The Wittig reaction of 2′-ketouridine (**129b**) with $Ph_3P = CHCO_2Bu\text{-}t$ gave exclusively (*Z*)-2′-[(alkoxycarbonyl)methylene]uridine derivative (**135**) in 95% yield. Addition of KSPh to **135** in a mixed solvent of dioxane/DMF (5:1) gave the α-phenylthio derivative in 69% yield. Compound **135** was converted to the (*E*)-*t*-butoxycarbonylmethyleuridine derivative **137** in four steps with 54% overall yield. Desilylation of **135** and **137** followed by acidic hydrolysis gave (*Z*)-**136** and (*E*)-**136** in high yields.

The syntheses of allenic nucleosides: 2′-deoxy-2′-(ethenylidene)cytidine (**141**) and 2′-deoxy-2′-(ethenylidene)adenosine (**145**) from 2′-ketonucleosides **78** and **91b** were reported by Jarvi *et al.*[71] Trimethylsilylethynyl magnesium bromide was added to 2′-ketonucleoside **78,** and the resulting tertiary alkoxide was quenched with methyl chloroformate to form the acetylenic carbonate **138** in 55% yield. Selective removal of the trimethylsilyl group from **138** was achieved with silver nitrate and potassium cyanide in 56% yield. Treatment of **139** with ammonium formate, a catalytic amount of $Pd_2(dba)_3$, and tributylphosphine resulted in the formation of 2′-allenic nucleoside derivative **140**. Desilylation followed by amination of **140** gave 2′-deoxy-2′-(ethenylidene)cytidine (**141**) (*Scheme 49*).[71]

Similarly, trimethylsilylethynyl magnesium bromide was also added to 2′-ketonucleoside **91b** to yield the corresponding tertiary alcohol in 94% yield (*Scheme 50*).



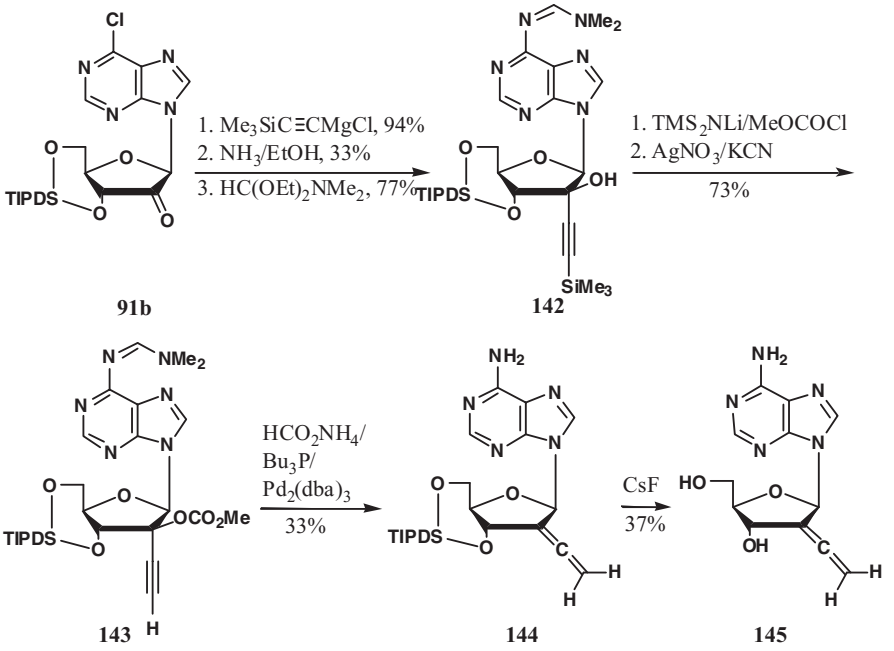
Scheme 48



Scheme 49

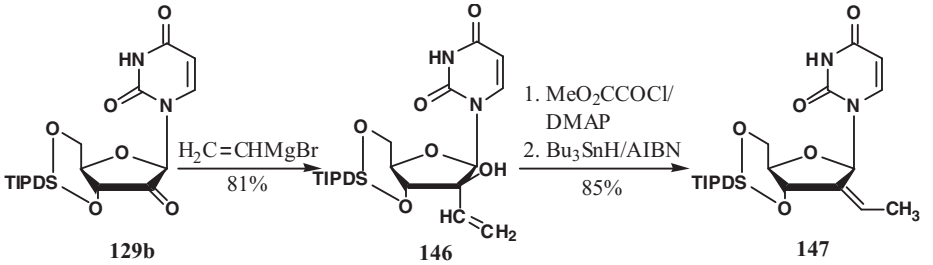
Amination of the 6-chloro group with ammonia in ethanol followed by dimethylaminomethylene protection gave **142** in about 25% yield. Tertiary alcohol **142** was converted to the carbonate *via* the alkoxide anion; the acetylenic trimethylsilyl group was removed with $AgNO_3$-KCN to provide **143** in 73% yield. Conversion to the allene as described above also resulted in loss of the N-6 amino protection group, giving **144** in 33% yield. Deprotection of **144** with CsF gave 2′-deoxy-2′-(ethenylidene)adenosine (**145**) (*Scheme 50*).[71]

Similarly, Iino *et al.* synthesized 2′-deoxy-2′-ethylidene derivative **147** (85% yield) by the deoxygenation of 2′-vinylarabinouridine derivative **146**.[72] The double bond shifted to



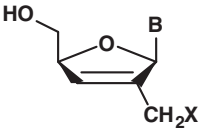
Scheme 50

form the more stable isomer during the radical deoxygenation. Compound **146** could be easily prepared in 81% yield by the addition of vinylmagnesium bromide to 2′-ketouridine **129b** with (*Scheme 51*).



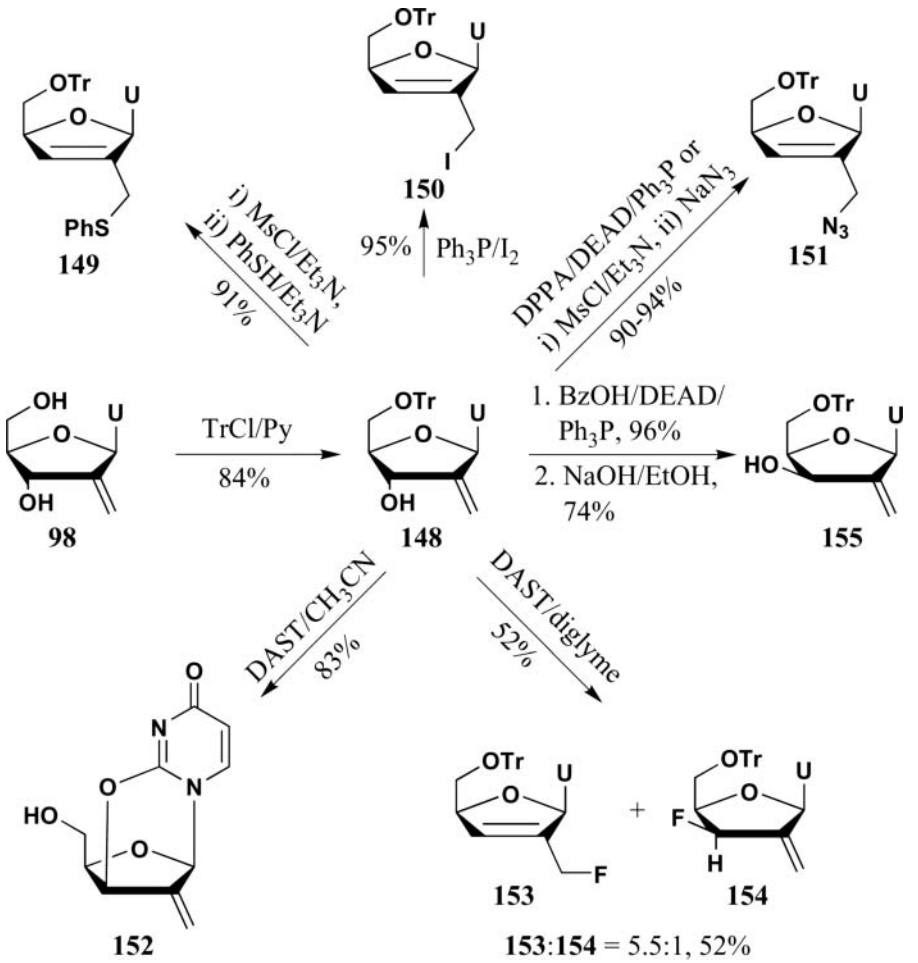
Scheme 51

*c) 2′,3′-Didehydro-2′,3′-dideoxy-2′-*C*-(methyl substituted) Nucleosides*



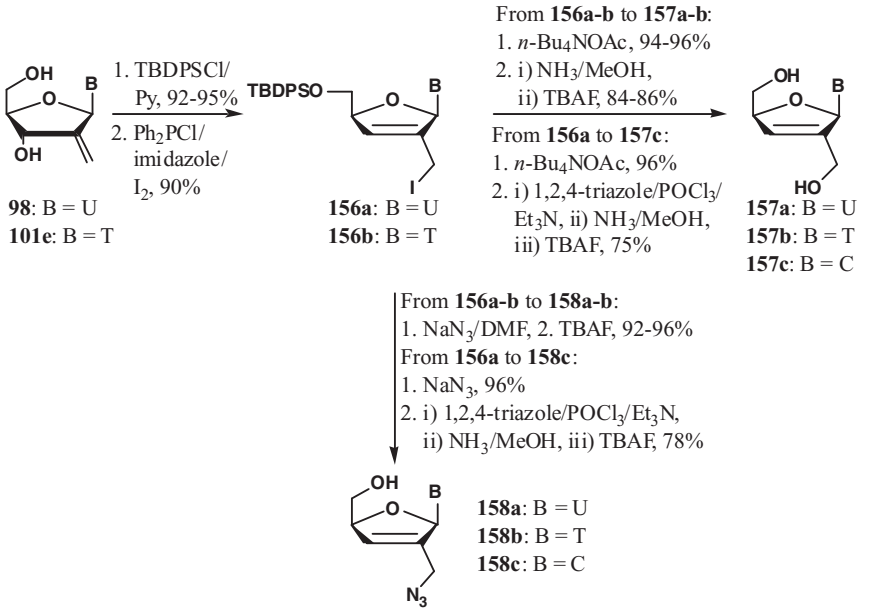
2′-*C*-Methyleneuridine (**98**) were selectively tritylated to give 5′-*O*-trityl-2′-*C*-methyleneuridine (**148**) in 84% yield. The 2′-*C*-methylene uridine derivative (**148**) could

be converted to a series of 2′,3′-didehydro-2′,3′-dideoxy-2′-*C*-methylsubstituted nucleosides in high yields *via* S_N2' type reactions (*Scheme 52*).[62,73] Reaction of **148** with $MsCl/Et_3N$ followed by substitution with thiophenol gave 2′,3′-didehyro-2′,3′-dideoxy-2′-phenylthiomethyluridine derivative **149** in 91% yield. Reaction of **148** with Ph_3P/I_2 gave 2′,3′-didehyro-2′,3′-dideoxy-2′-iodomethyluridne derivative **150** in 95% yield. The corresponding 2′-azidomethyl-2′,3′-didehydro-2′,3′-dideoxyuridne derivative **151** was obtained from **148** either under Mitsunobu reaction conditions with diphenylphosphoryl azide (DPPA) or *via* a two-step reaction sequence (reaction with $MsCl/Et_3N$, then with NaN_3) in 90–94% yield. Solvents had a large effect on the reaction of **148** with DAST. For example, reaction in acetonitrile gave the O^2,3′-anhydro derivative **152** in 83% yield, and the reaction in diglyme gave a mixture of 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoromethyluridine (**153**) and 3′-fluoro-2′-methyleneuridine (**154**) in 52% yield (5.5:1 ratio **153**/**154**). The 2′-*C*-methyleneuridine derivative **148** could be also converted to its 3′-β-isomer **155** in two steps with 71% overall yield.



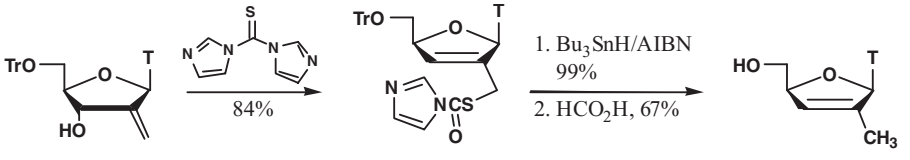
Scheme 52

Protection of the primary hydroxyl group of **98** and **101e** as the *tert*-butyldiphenylsilyl (TBDPS) ether followed by iodination with Ph_2PCl/imdazole/iodine gave the S_N2' reaction products: 2′,3′-didehydro-2′,3′-dideoxy-2′-iodomethyl pyridmidine nucleoside derivatives **156a** and **156b** in high yields (*Scheme 53*).[74] The 2′-iodomethyl nucleoside derivatives **156a–b** could be converted to 2′,3′-didehydro-2′,3′-dideoxy-2′-hydroxymethyluridine (**157a**) and thymidine (**157b**) in high yields (three chemical steps: S_N2 substitution with AcO^-, deacetylation with ammonia, and desilyaltion with TBAF). The cytidine derivative (**157c**) was synthesized from **156a** in four steps. By the similar reaction sequence, the 2′-azidomethyl-2′,3′-didehydro-2′,3′-dideoxyuridine, thymidine and cytidine **158a–c** were synthesized from **156a–b** in high yield.



Scheme 53

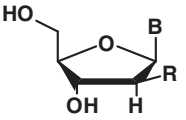
Treatment of 5′-*O*-trityl-2′-*C*-methylene-5-methyluridine (**159**) with 1,1′-thiocarbonyldiimidazole in DMF gave the allylic rearranged product **160** in 84% yield. **160** was heated with *n*-Bu_3SnH in the presence of AIBN in toluene to give 2′,3′-didehydro-2′,3′-dideoxy-2′-methyl-5′-*O*-trityl-5-methyluridine in 99% yield. Deprotection with formic acid furnished the synthesis of 2′,3′-didehydro-2′,3′-dideoxy-2′-methyl-5-methyluridine (**161**) in 67% yield (*Scheme 54*).[60]



159 **160** **161**

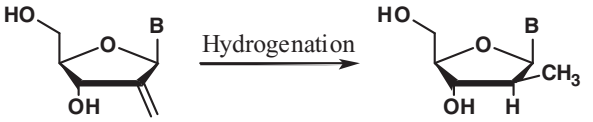
Scheme 54

III. 2′-*C*-*β*-Branched-2′-Deoxynucleosides

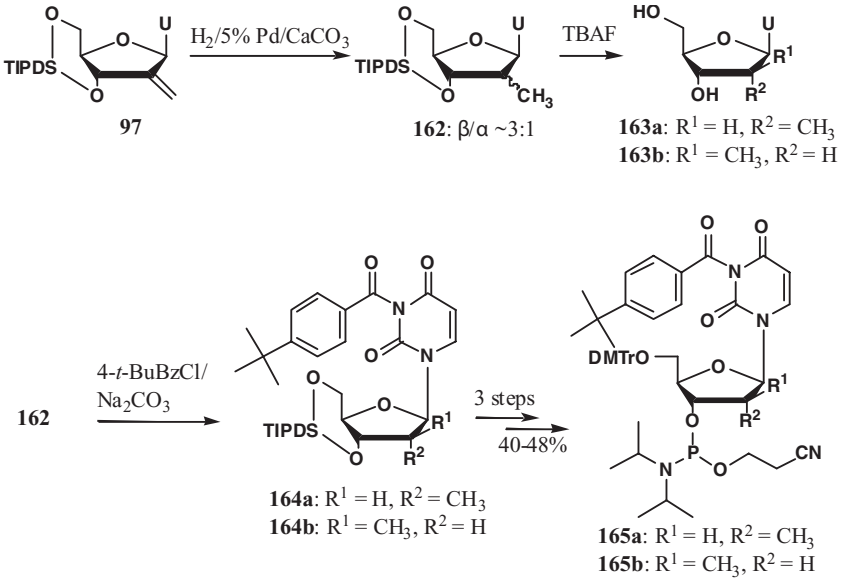


1. 2′-C-β-Methyl-2′-deoxynucleosides

a) Synthesis via *Hydrogenation of 2′-C-Methylene-2′-deoxynucleosides*

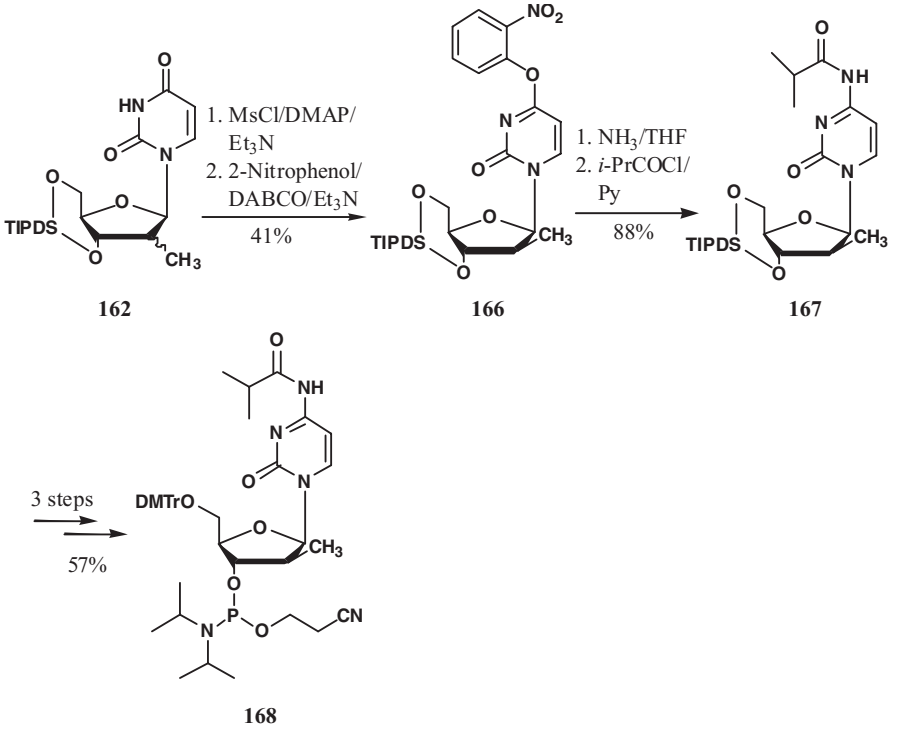


Cicero reported that hydrogenation of 2′-*C*-methyleneuridine derivative **97** using 5% Pd on $CaCO_3$ gave a mixture of 2′-*C*-*α*/*β*-methyluridine derivatives **162** (*β*/*α* ~3:1).[75] Deprotection of **162** with TBAF gave 2′-*C*-*β*-methyl-2′-deoxyuridine (**163b**) and 2′-*C*-*α*-methyl-2′-deoxyuridine (**163a**), which could be separated by silica gel chromatography.[75] The *α*- and *β*-isomers of **162** could be separated only after conversion to the N^3-(4-*tert*-butylbenzoyl) nucleoside derivatives (**164a** and **164b**). The *β*-isomer **164b** and the *α*-isomer **164a** were converted into the corresponding phosphoramidites **165a** (48% yield) and **165b** (40% yield) in three steps *via* desilylation, 5′-DMTr protection and 3′-phosphitylation (*Scheme 55*).[76]



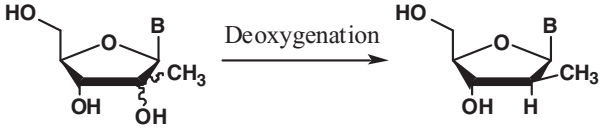
Scheme 55

The phosphoramidite derivative of 2′-*C*-*β*-methylcytidine (**168**) could also be prepared from **162**. If **162** was treated with MsCl followed by 2-nitrophenol and diazabicyclo[2,2,2]octane, the reaction afforded the two diasteromers of the corresponding O^4-nitrophenylnucleosides. This mixture could be resolved by silica gel chromatography to afford pure compound **166** in 41% yield. Amination followed by acylation converted **166** into the cytidine derivative **167** in 88% yield. Desilylation of **167** followed by 5′-DMTr protection and 3′-phosphitylation gave the phosphoramidite (**168**) in 57% yield (*Scheme 56*).[76]



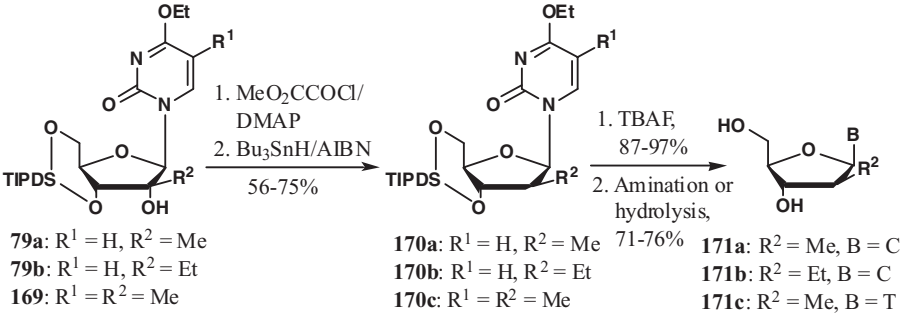
Scheme 56

b) Synthesis via *Deoxygenation of 2′*-C-*Methylribonucleosides or 2′*-C-*Methylarabinonucleosides*



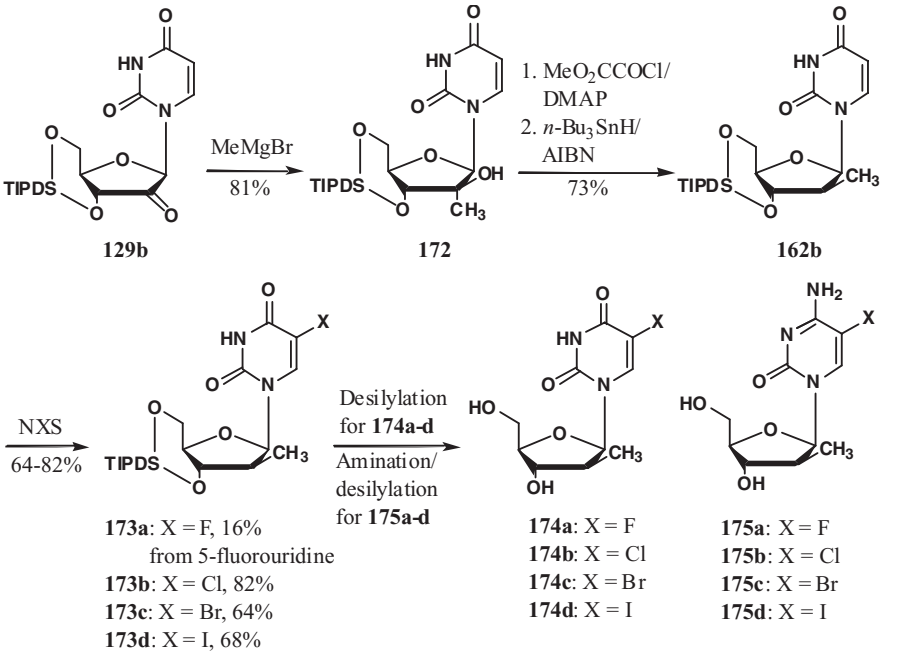
The 2′-*C*-branched ribonuceloside derivatives **79a–b** and **169** were obtained as minor products by the reaction of the corresponding 2′-ketonucleosides with organometallic reagents.[8] Reaction of **79a–b** or **169** with MeO_2CCOCl/DMAP followed by Bu_3SnH/AIBN gave 2′-*C*-*β*-branched-2-deoxynucleoside derivatives **170a–c** in 56–75% yield.

Desilylation of **170a–c** with TBAF followed by amination or hydrolysis gave 2′-*C*-β-methyl-2′-deoxycytidine (**171a**), 2′-*C*-β-ethyl-2′-deoxycytidine (**171b**) and 2′-*C*-β-methylthymidine (**171c**) in good yields (*Scheme 57*).[7,10]



Scheme 57

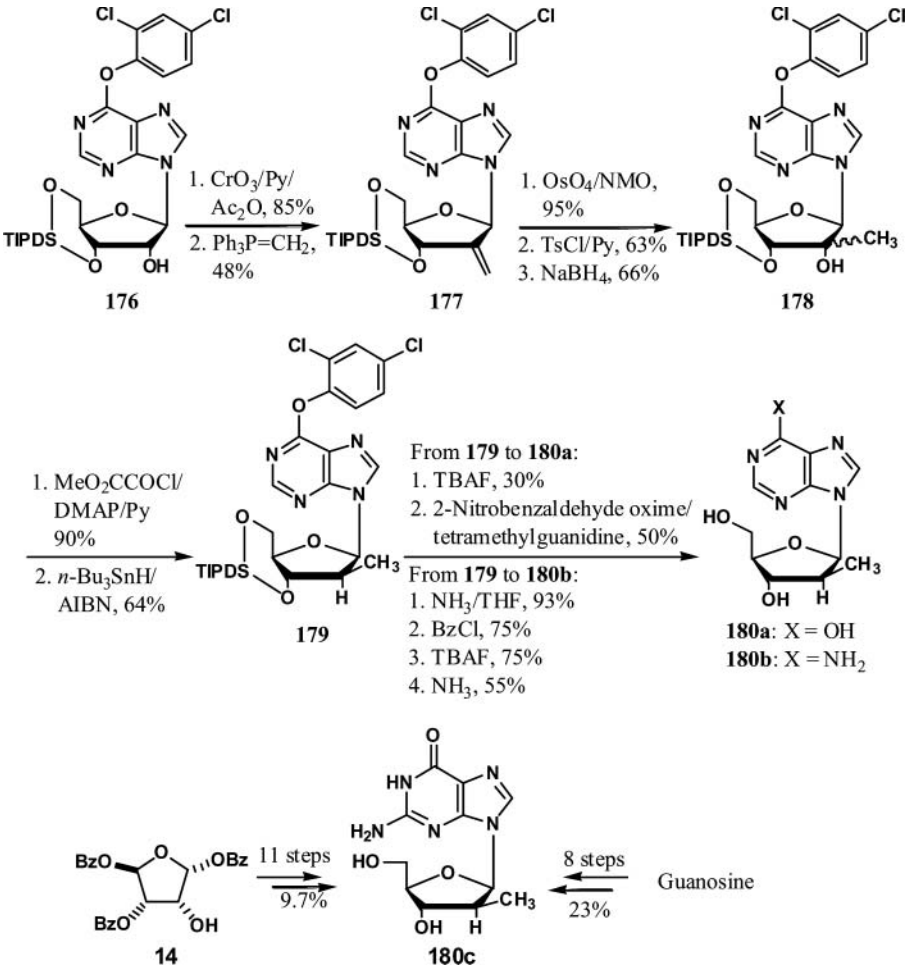
Awano *et al.* reported the syntheses of 5-halo-2′-*C*-β-methyl-2′-deoxypyrimidine nucleosides (uridine and cytidine) starting from uridine or 5-fluorouridine (*Scheme 58*).[14] The 2′-ketouridine derivative **129b** reacted with methylmagnesium bromide to give 2′-methylarabinonucleoside derivatives **172** in 81% yield. Deoxygenation of **172** using MeO_2CCOCl/DMAP followed by *n*-Bu_3SnH/AIBN gave **162b** (the β-isomer of **162**) in 73% yield. The 5-fluoro-2′-methyl-2′-deoxyuridine derivative **173a** was prepared from 5-fluorouridine in four steps (16% overall yield). **162b** could be halogenated with NXS (X = Cl, Br, I) to give the 5-halogenated derivatives (**173b–d**) in 64–82% yield.



Scheme 58

Desylilation of **173a–d** with TBAF gave the 5-halogenated 2′-deoxy-2′-C-β-methyluridine (**174a–d**) in high yield. Transformation of **173a–d** into the cytidine analogues followed by TBAF-desilylation gave 5-halogenated 2′-deoxy-2′-*C*-β-methyluridine (**175a–d**) in good yields.

2′-Deoxy-2′-*C*-β-methylpurine nucleosides such as 2′-deoxy-2′-*C*-β-methyl adenosine **180b** and 2′-deoxy-2′-*C*-β-methylinosine **180a** as well as the corresponding phosphoramidites were synthesized by Caballero *et al. via* 2′-deoxygenation of 2′-*C*-methylpurine nucleosides **178** (*Scheme 59*).[77] 6-*O*-(2,6-Dichlorophenyl)-3′,5′-*O*-TIPDS-inosine (**176**)[78] was oxidized to the 2′-ketonucleoside in 85% yield. Wittig olefination of the 2′-ketonucleoside with methylenetriphenylphosphonium gave 2′-methylpurine nucleoside **177** in 48% yield. However, the simple hydrogenation of **177** with Pd/C as catalyst did not give the 2′-deoxy-2′-*C*-methylpurine derivative. Instead, the 2′-methylenepurine riboside **177** was oxidized with OsO_4 as catalyst, producing a diastereoisomeric mixture of the corresponding diols in a 10:1 ratio. The mixture of

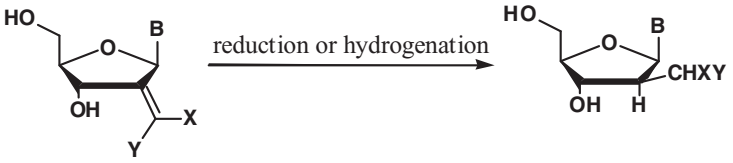


Scheme 59

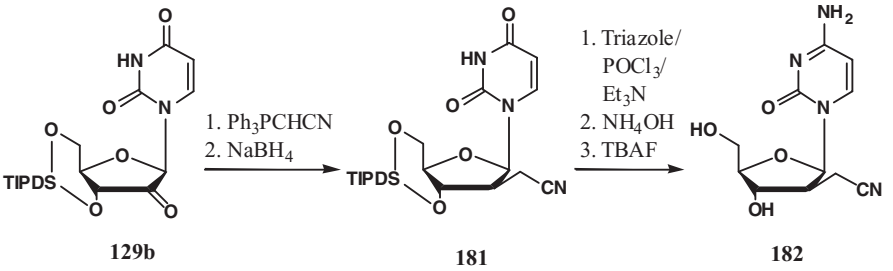
diastereoisomers was then selectively tosylated at the primary alcohol moiety; subsequent reduction with $NaBH_4$ gave 2′-*C*-methylpurine nucleosides **178** in 42% overall yield as a mixture of diastereoisomers. Reaction of **178** with methoxalyl chloride in the presence of DMAP furnished the corresponding mixture of esters in 90% yield. Reduction of the crude product by *n*-Bu_3SnH in dried toluene with AIBN as a radical initiator gave 2′-*C*-*β*-methylpurine nucleoside **179** in 64% yield. **179** was converted to 2′-deoxy-2′-*C*-*β*-methylinosine (**180a**) and 2′-deoxy-2′-*C*-*β*-methyladenosine (**180b**) in 15% and 29% yields, respectively. Similarly, 2′-deoxy-2′-*C*-*β*-methylguanosine (**180c**) could be prepared by 2′-radical deoxygenation of 2′-*C*-methylguanosine or 2′-*C*-methylarabinonucleosides starting from 1,3,5-tri-*O*-benzoyl-*α*-D-ribofuranose or guanosine in good yields.[79]

2. 2′-C-β-(Substituted Methyl)-2′-deoxynucleosides

a) Synthesis via *Reduction or Hydrogenation of 2′-C-(Substituted Methylene) Nucleosides*



Yoshimura *et al.* reported the synthesis of 2′-*C*-*β*-cyanomethyl-2′-deoxycytidine (**182**) from 2′-ketouridine (**129b**) (*Scheme 60*).[5] Wittig reaction of 2′-ketouridine **129b** with cyanomethylenetriphenylphosphorane followed by reduction with sodium borohydride gave the 2′-*C*-*β*-cyanomethyl-2′-deoxyuridine derivative (**181**). Transformation of **181** into 2′-*C*-*β*-cyanomethyl-2′-deoxycytidine (**182**) was achieved in three steps using standard reaction sequences.

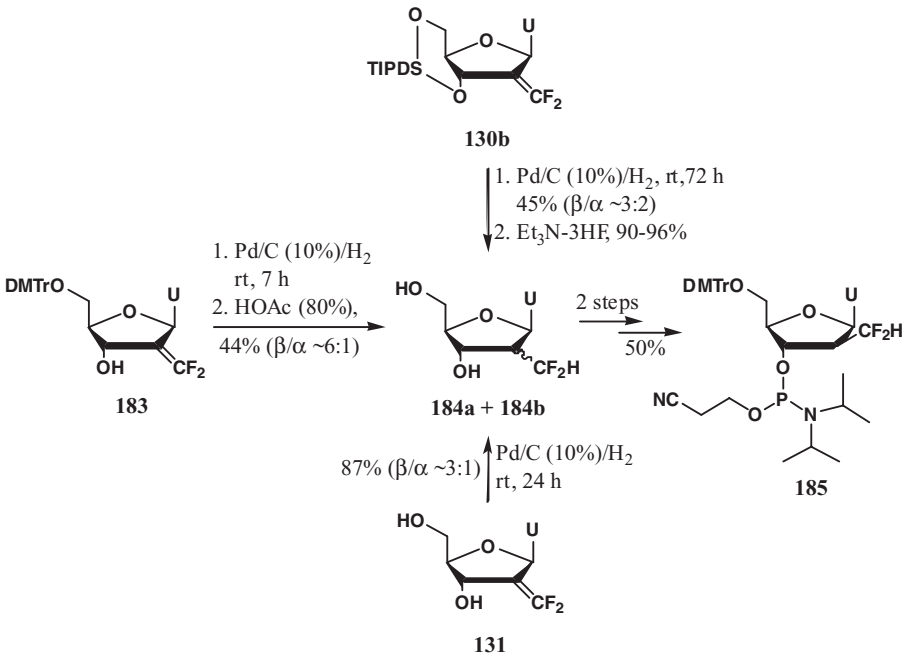


129b **181** **182**

Scheme 60

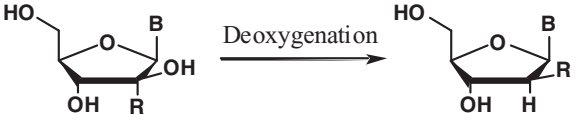
2′-*C*-*β*-Difluoromethyl-2′-deoxyuridine (**184b**) and its phosphoramidite (**185**) were obtained *via* hydrogenation of the 2′-difluoromethleneuridine derivatives **130b**, **131**, and **183** (*Scheme 61*). Serafinowski *et al.* reported that 5′-*O*-DMTr-2′-difluoromethyleneuridine (**183**) was hydrogenated followed by detritylation to give **184b** along with a small amount of the *α*-isomer **184a** in 44% overall yield (*β*/*α* ~6:1).[80,81] However, the hydrogenation of 3′,5′-*O*-TIPDS-2′-difluoromethyleneuridine (**130b**) was rather slow (room temperature, 72 h) and resulted in low yield (45%) and low selectivity (*β*/*α* 3:2).[80] Hydrogenation of **131**, which was obtained from desilylation of **130b**, gave 2′-*C*-*β*-difluoromethyl-2′-deoxyuridine

(**184b**) in good yield (87%) with good selectivity (β/α 3:1).[82] The 2′-*C*-β-difluoromethyl-2′-deoxyuridine (**184b**) was converted into the corresponding phosphoramidite (**185**) in two steps with 50% yield (*Scheme 61*).[80]



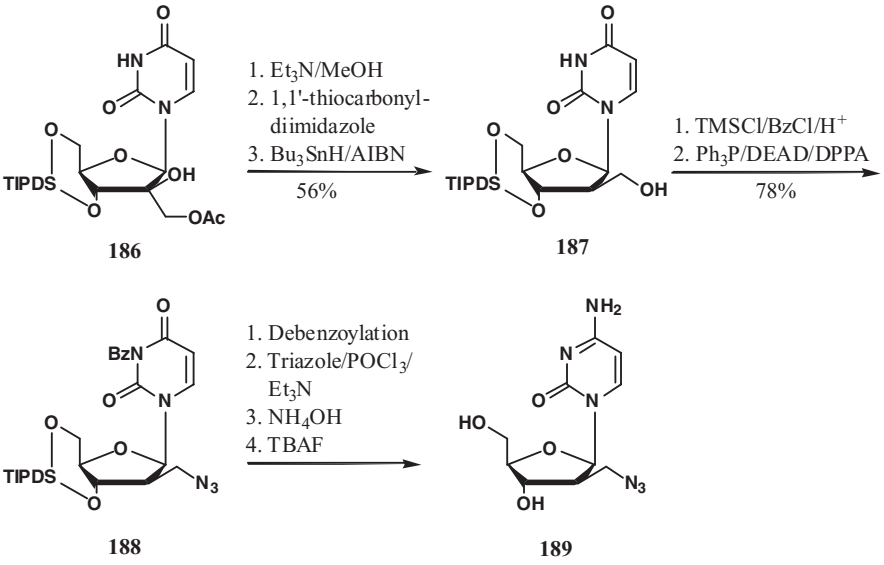
Scheme 61

b) Synthesis via *Deoxygenation of 2′*-C-*Branched Arabinonucelosides*



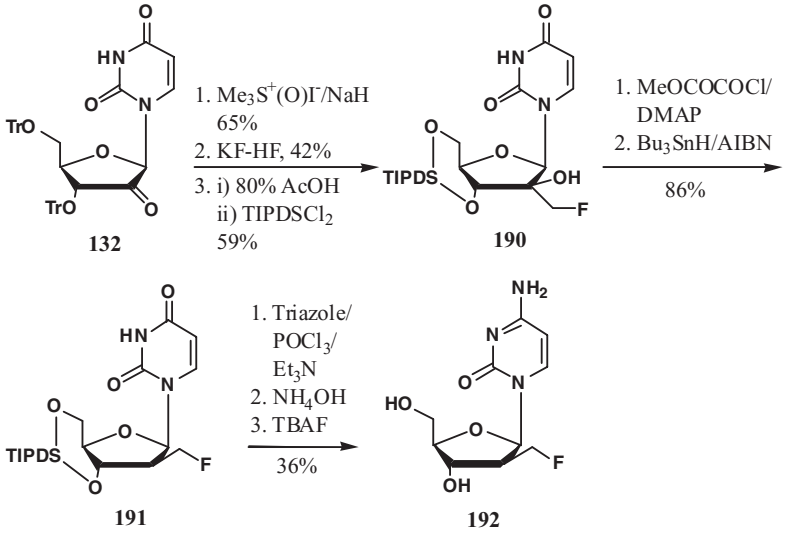
Yoshimura *et al.* synthesized 2′-*C*-β-azidomethyl-2′-deoxycytidine (**189**) from an arabinouridine derivative *via* radical deoxygenation (*Scheme 62*).[5] Compound **186**[83] was selectively deacetylated by triethylamine-MeOH to afford the diol. Following treatment with 1,1′-thiocarbonyldiimidazole to give a cyclic thiocarbonate, deoxygenation with tributyltin hydride in the presence of AIBN removed the hydroxyl group from the tertiary carbon center to give the 2′-β-hydroxymethyl-2′-deoxyuridine derivative **187**. For the introduction of the azido group within the 2′-branched chain, the aglycone had to be benzoylated at the N-3 position to avoid the formation of an anhydronucleoside. Selective N-3 benzoylation followed by Mitsunobu reaction using diphenyl phosphoryl azide as the azide source converted **187** to **188** in 78% yield. **188** could be converted to 2′-*C*-β-azidomethyl-2′-deoxycytidine (**189**) using the standard reaction sequence (debenzylation, amination and desilylation).

Yoshimura *et al.* also reported the synthesis of 2′-*C*-β-fluoromethyl-2′-deoxycytidine (**192**) from 2′-ketonucleoside **132** (*Scheme 63*).[12] **132** was converted to 2′-fluoromethyl



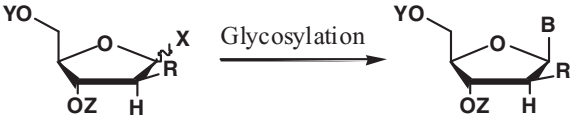
Scheme 62

arabinouridine derivative (**190**) in four steps with 16% overall yield. Deoxygenation of **190** with MeO_2CCOCl/DMAP and Bu_3SnH/AIBN gave 2′-*C*-*β*-fluoromethyl-2′-deoxyuridne (**191**) in 86% yield. Standard reaction sequences were used to transform uridine derivative **191** into 2′-*C*-*β*-cyanomethyl-2′-deoxycytidine (**192**) in 36% overall yield.

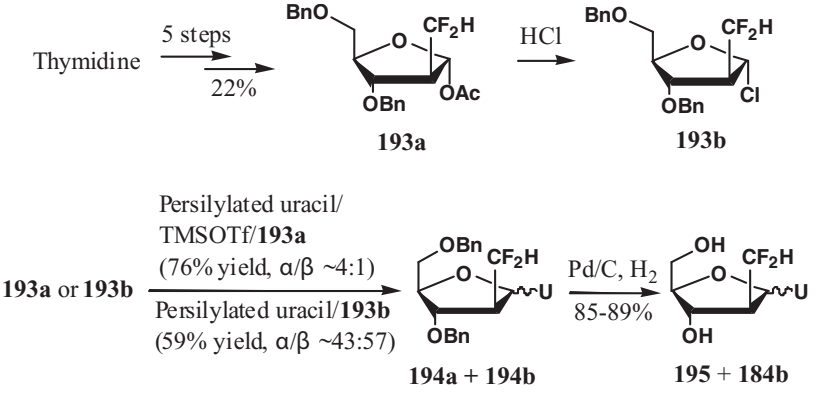


Scheme 63

c) Synthesis via *Glycosylation with 2-C-β-Branched-2-deoxyribose Derivatives*



Marcotte *et al.* synthesized 2′-*C*-*β*-difluoromethyluridine (**184b**) and 2′-*C*-*β*-difluoromethyl-*α*-uridine (**195**) by glycosylation with 2-*C*-*β*-difluoromethylribose derivatives **193a** and **193b**.[82] **193a** was prepared from thymidine in 22% overall yield (five steps). Treatment of **193a** with HCl gave 1-chloro-2-difluoromethyl sugar **193b**. Glycosylation of persilyated uracil with **193a** in the presence of TMSOTf gave a mixture of **194a** and **194b** in a ratio of *α*/*β* ~4:1. However, the ratio of **194a** to **194b** was decreased (*α*/*β* 43:57) with inverse selectivity when the 1-chlorosugar derivative was used. Catalyzed hydrogenated deprotection of **194b** and **194a** gave the 2′-*C*-*β*-difluoromethyluridine (**194b**) and 2′-*C*-*β*-difluoromethyl-*α*-uridine (**195**) in 89% and 85% yields, respectively (*Scheme 64*).

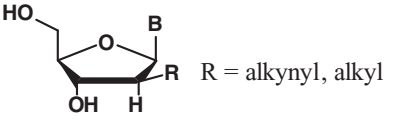


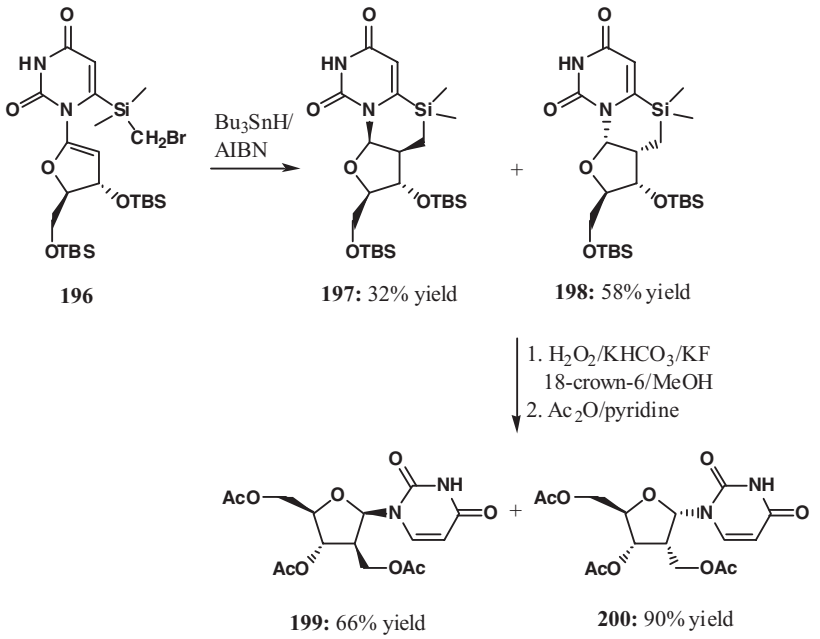
Scheme 64

d) Synthesis via *Intramolecular Radical Cyclization.*

Ogamino *et al.* obtained 3′,5′-di-*O*-acetyl-2′-*C*-*β*-acetoxymethyl-2′-deoxyuridine (**199**) by 6-*endo*-cyclization of 6-(bromomethyl)dimethylsilyl 1′,2′-unsaturated uridine (**196**) (*Scheme 65*).[84] Radical reaction of **196** was carried out in refluxing benzene by addition of a mixture of Bu_3SnH and AIBN, giving the 6-endo-cyclized products **197** (32%) and **198** (58%). Oxidative cleavage of **197** and **198** with H_2O_2/K_2CO_3/KF/18-crown-6 in refluxing methanol followed by acetylation gave 2′-*C*-*β*-acetoxymethyl-2′-deoxyuridine (**199**) and a diastereoisomer **200** in 66% and 90% yields, respectively.

3. 2′-C-β-Alkynyl/alkyl-2′-deoxynuclosides





196 **197:** 32% yield **198:** 58% yield

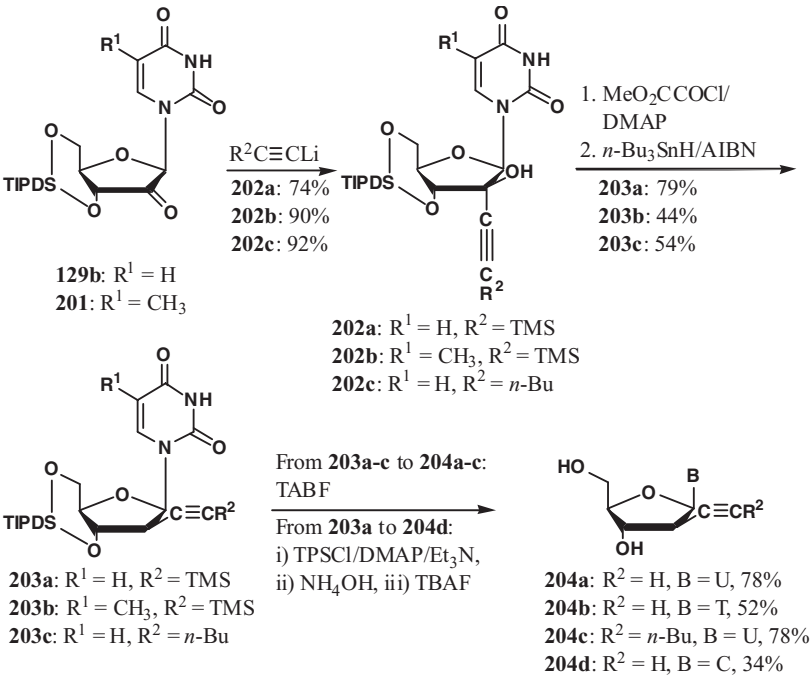
199: 66% yield **200:** 90% yield

Scheme 65

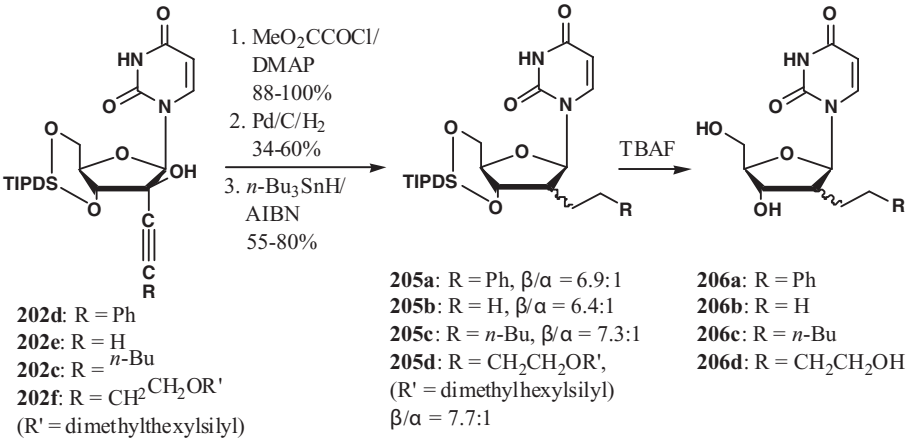
Alkynyllithium reagents were added to 2′-ketopyrimidine nucleosides **129b** and **201** to generate the corresponding 2′-*C*-α-alkynyl-2′-arabinonucleosides **202a–c** in 74–92% yield (*Scheme 66*). Deoxygenation of **202a–c** was achieved by the reactions with methyl chlorooxate/DMAP followed by tributyltin hydride/AIBN to give the 2′-*C*-β-alkynyl-2′-deoxynuclosides derivatives (**203a–c**) in 44–79% yield. Desilylation of **203a-c** with TBAF generated 2′-*C*-β-alkynyl-2′-deoxypyrimidine nucleosides **204a–c** in 52–78% yields. The uridine derivative **203a** was also converted into the corresponding cytidine derivative **204d** in 34% overall yield (three steps) (*Scheme 66*).[72,85]

The 2′-*C*-alkynylarabinouridines **202c–f** have been used to synthesize 2′-*C*-alkyl-2′-deoxyuridines **206a–d** (β/α ~7:1).[86] 2′-*C*-Alkynylarabinonucleoside (**202c-f**) were converted into compounds **205a–d** in good yield and good selectivity in three steps *via* oxo-ester formation, palladium catalyzed hydrogenation and radical deoxygenation. Desilylation of **205a–d** with TBAF gave 2′-*C*-β/α-alkyl-2′-deoxyuridines **206a–d** (*Scheme 67*).

The 2′-deoxy-2′-*C*-β-ethynylpurine nucleosides, **210a** and **210b**, were prepared by Buff *et al.* from adenosine and guanosine (*Scheme 68*).[87] Dess-Martin oxidation of **207a–b** followed by trimethylsilylethynyllithium addition gave 2′-trimethylsilylethynylarabinopurine nucleoside derivatives **208a** and **208b** in 91% and 80% yields, respectively. 2′-Deoxygenation of the oxoate esters of **208a–b** with *n*-Bu_3SnH/AIBN yielded the corresponding 2′-deoxy-2′-*C*-β-trimethylsilylethynylpurine nucleosides **209a–b** in 65–67% yield. Interestingly, the reaction still gave 2′-deoxy-2′-*C*-β-trimethylsilylethynyladenosine (**209a**) in 67% yield even though the benzoyl protecting group on the adenine ring was lost during the deoxygenation process. However, the dimethylaminomethylene protecting group on the guanine ring was stable during the two-step deoxygenation procedure. Desilylation of **209a–b** with TBAF/AcOH followed by removal

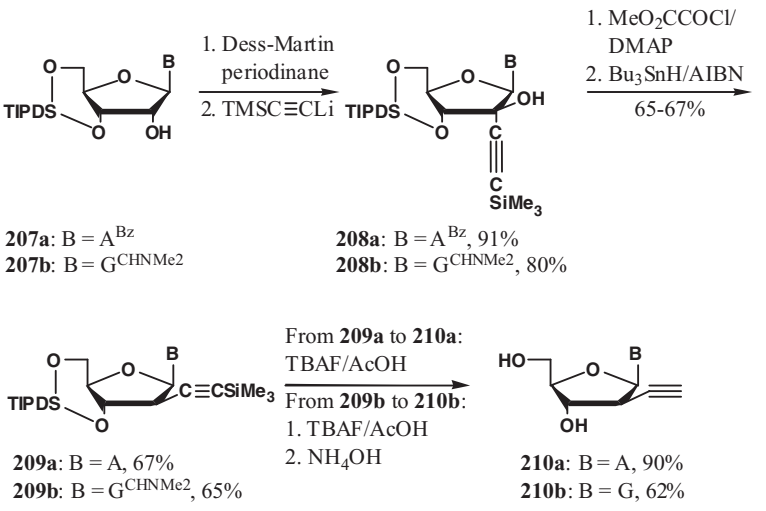


Scheme 66



Scheme 67

of the dimethylaminomethylene group using ammonium hydroxide gave 2′-deoxy-2′-*C*-*β*-ethynyladenosine (**210a**) and 2′-deoxy-2′-*C*-*β*-ethynylguanosine (**210b**) in 90% and 62% yields, respectively. Buff *et al.* then prepared all five phosphoramidites of the 2′-deoxy-2′-*C*-*β*-ethynylnucleosides (A, C, G, T, U) and incorporated them into oligonucleotides *via* solid phase synthesis.[87]



207a: B = A^{Bz}
207b: B = G^{CHNMe2}

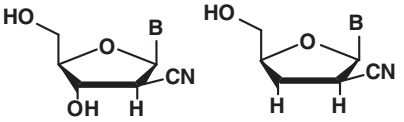
208a: B = A^{Bz}, 91%
208b: B = G^{CHNMe2}, 80%

209a: B = A, 67%
209b: B = G^{CHNMe2}, 65%

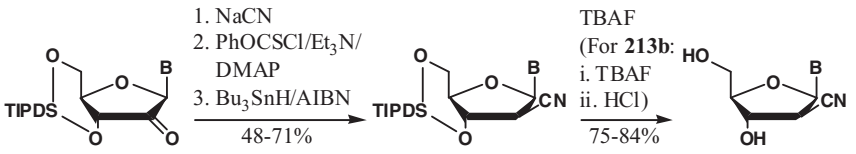
210a: B = A, 90%
210b: B = G, 62%

Scheme 68

4. 2′-C-β-Cyano-2′-deoxynuclosides and 2′-C-β-Cyano-2′,3′-dideoxynuclosides



Azuma *et al.* reported that addition of 2′-cyano anion to the 2′-ketoribonucleoside derivatives **211a**, **211b**, **129b** and **201** yields a mixture of 2′-cyanoribonucleosides and 2′-cyanoarabinonucleosides. Radical deoxygenation of the 2′-hydroxyl group gave 2′-*C*-β-cyano-2′-deoxyribonucleoside derivatives **212a–d** in 48–71% yield (*Scheme 69*).[11,88] Desilylation of **212a**, **212c** and **212d** with TBAF gave the free 2′-*C*-β-cyano-2′-deoxynuclosides **213a**, **213c** and **213d** in 76–83% yield. For the cytidine derivative **212b**, desilylation with TBAF followed by removal of the N^4-acetyl group with HCl in methanol converted **212b** to the corresponding cytidine derivative **213b** in 75% yield (two steps). 2′-β-Cyano-2′-deoxyadenosine **213a** and 2′-β-cyano-2′-deoxyuridine **213c**) were also prepared by Velazquez and Camarasa *via* the same reaction sequences.[89]



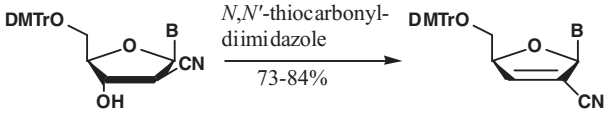
211a: B = A
211b: B = C^{Ac}
129b: B = U
201: B = T

212a: B = A, 67%
212b: B = C^{Ac}, 57%
212c: B = U, 48%
212d: B = T, 71%

213a: B = A, 83%
213b: B = C, 75%
213c: B = U, 76%
213d: B = T, 78%

Scheme 69

Attempts to synthesize 2′-*C*-*β*-cyano-2′,3′-dideoxynuclosides *via* the deoxygenation of 2′-*β*-cyano-2′-deoxynucleosides were not successful.[88] Instead, reaction of 2′-*β*-cyano-2′-deoxynucleoside derivatives **214a** and **214b** with *N*,*N*′-thiocarbonyldiimidazole in DMF at room temperature resulted in the formation of 2′-*C*-cyano-2′,3′-didehydro-2′,3′-dideoxynucelosides **215a–b** in high yield (*Scheme 70*).

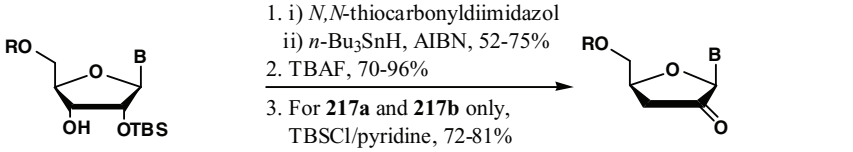


214a: B = C^{Ac}
214b: B = T

215a: B = C^{Ac}, 73%
215b: B = T, 84%

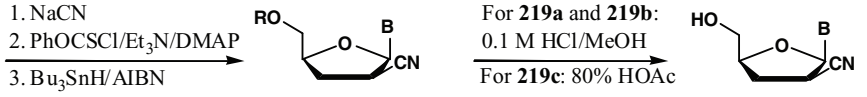
Scheme 70

2′-*C*-*β*-Cyano-2′,3′-dideoxynuclosides were prepared from the corresponding 3′-deoxy-2′-ketonucleosides **217a–c** by Velazquez and Camarasa (*Scheme 71*).[89] The 2′, 5′-bis-*O*-silylated derivatives of uracil (**216a**), 4-*N*-MMTr-cytosine (**216b**) and 5′-MMTr-2′-*O*-silylated derivative of adenine (**216c**) were deoxygenated by treatment with *N*,*N*-thiocarbonyldiimidazol followed by reaction with Bu_3SnH/AIBN to give the 3′-deoxyderivatives in 52–75% yield. Treatment with TBAF afforded the corresponding 3-deoxyribonucelosides in 70–96% yield. Reaction of 3′-deoxyuridine and 3′-deoxycytidine with 1 eq. of *t*-butyldimethylsilyl chloride in dry pyridine gave 5′-*O*-silylated 3′-deoxyuridine and 3′-deoxycytidine in 72% and 81% yields, respectively. Oxidation of 5′-*O*-protected nucleosides with CrO_3/pyridine/Ac_2O afforded the 2′-ketonucleosides **217a–c** in 53–89% yield. Treatment of **217a–c** with sodium cyanide gave a mixture of the epimeric nucleoside 2′-cyanohydrins. Further treatment of the mixture with (phenoxy)thiocarbonyl chloride and DMAP followed by reaction with Bu_3SnH/AIBN gave the 2′-*C*-cyano-2′,3′-



216a: R = TBS, B = U
216b: R = TBS, B = C^{MMTr}
216c: R = MMTr, B = A

217a: R = TBS, B = U
217b: R = TBS, B = C^{MMTr}
217c: R = MMTr, B = A



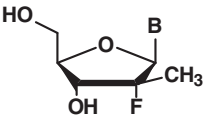
218a: R = TBS, B = U, 50%
218b: R = TBS, B = C^{MMTr}, 36%
218c: R = MMTr, B = A, 25%

219a: B = U, 86%
219b: B = C, 80%
219c: B = A, 70%

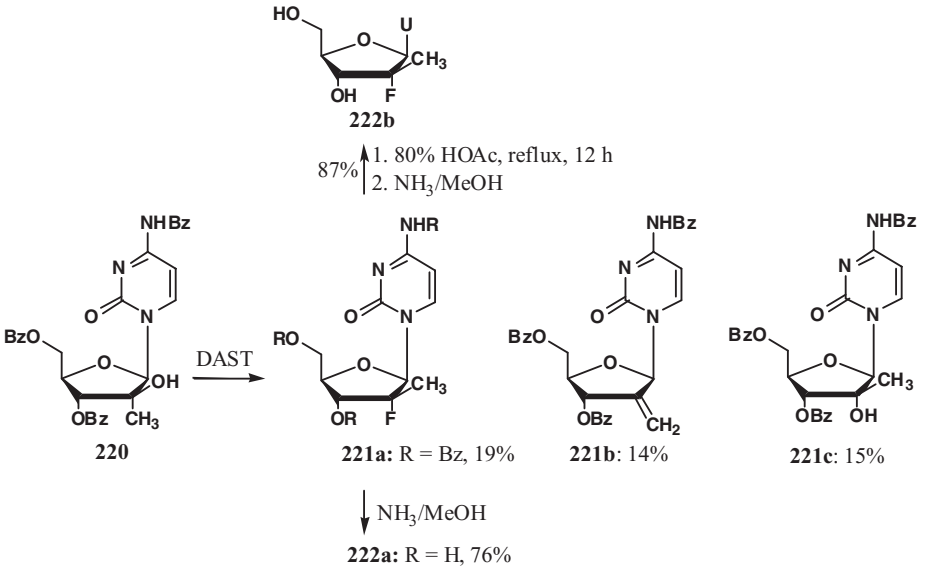
Scheme 71

dideoxyderivatives **218a–c** in 25–50% yield. Deprotection of **218a–c** under acidic conditions gave 2′-*C*-β-cyano-2′,3′-dideoxynucleosides **219a–c** in 70–86% yield.

5. 2′-Deoxy-2′-α-fluoro-2′-C-β-methylnuclosides

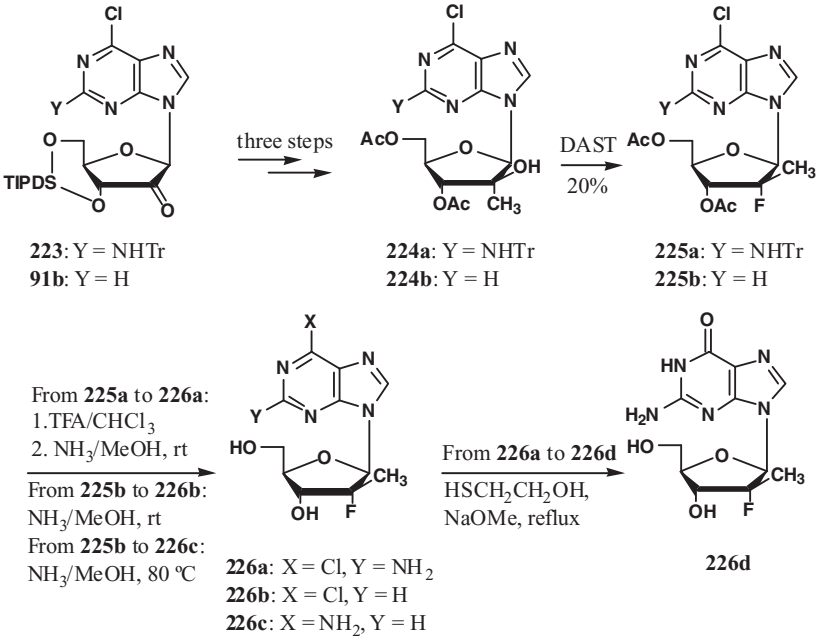


For the synthesis of 2′-deoxy-2′-fluoro-2′-*C*-methylcytidine (**222a**), N^4-benzoyl-1-(2-methyl-3,5-di-*O*-benzoyl-β-D-arabinofuranosyl]cytidine (**220**) was chosen by Clark *et al.* as the key intermediate and prepared in approximately 20% yield in six steps from cytidine (*Scheme 72*).[90] Upon treating **220** with DAST in toluene or dichloromethane, a clean mixture of three products (**221a–c**) in 14–19% yield for each compound was obtained. Hydrolysis of **221a** with ammonia in methanol gave 2′-deoxy-2′-fluoro-2′-*C*-methylcytidine (**222a**: 76% yield). 2′-Deoxy-2′-fluoro-2′-*C*-methyluridine (**222b**) was prepared from **221a** by deamination in refluxing 80% acetic acid followed by debenzoylation with ammonia in methanol in 87% yield.



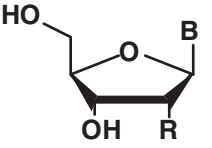
Scheme 72

Clark *et al.* also reported the synthesis of 2′-deoxy-2′-fluoro-2′-*C*-methylpurines **226a–d** from 2′-ketopurines **223** and **91b**.[17] The arabinopurines **224a–b** could be prepared from **223** and **91b** in three steps: methyl addition, desilylation and acetylation. The reaction of **224a–b** with DAST gave compounds **225a**–**b** in about 20% yield. Hydrolysis as well as aminolysis gave 2′-deoxy-2′-fluoro-2′-*C*-methylpurines **226a–d** as shown in *Scheme 73*. The yield in each step was not reported.

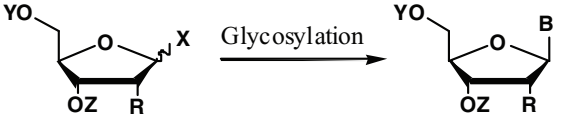


Scheme 73

IV. 2′-*C*-α-Branched-2′-Deoxynucleosides

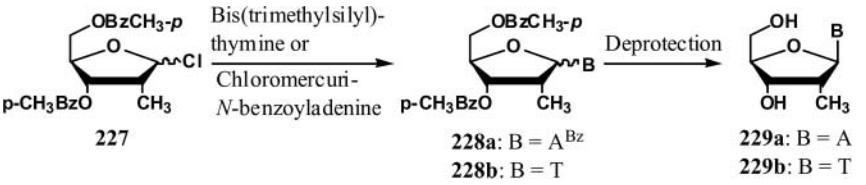


1. Synthesis via *Glycosylation with 2-*C*-α-Branched-2-deoxyribose Derivatives*



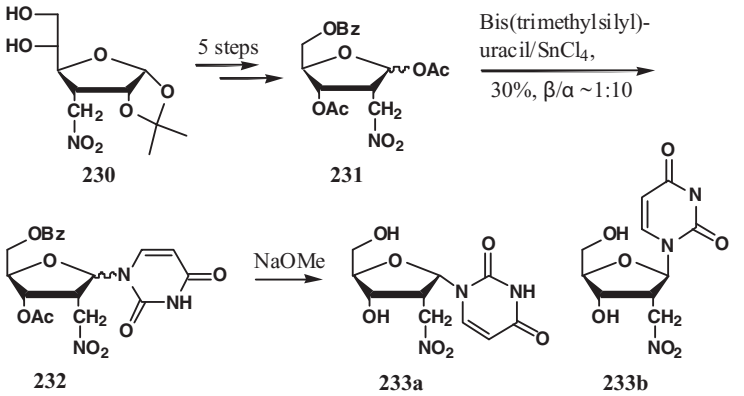
Glycosylation of persilylated nucleobases with 2-*C*-α-branched-2-deoxyribose derivatives in the presence of Lewis acids generally generates a mixture of anomers. For example, Novak *et al.* prepared 2′-*C*-α-methyl-2′-deoxyadenosine (**229a**) and thymidine (**229b**) from a 1-chloro-2-α-methyl-2-deoxyribose derivative (**227**) (*Scheme 74*).[91] Compound **227** was prepared from 2-*C*-β-methyl-D-ribono-γ-lactone in six steps. Glycosylation of chloromercuri-*N*-benzoyladenine or persilylated thymine with **227** generated a mixture of anomers of 2′-*C*-α-methyladenosine and thymidine derivatives (**228a** and **228b**), respectively. Hydrolysis of the β-anomers of **228a** and **228b** yielded the corresponding 2′-*C*-α-

methyl nucleoside derivatives **229a** and **229b**. The yield and selectivity of the glycosylation reactions were not described.



Scheme 74

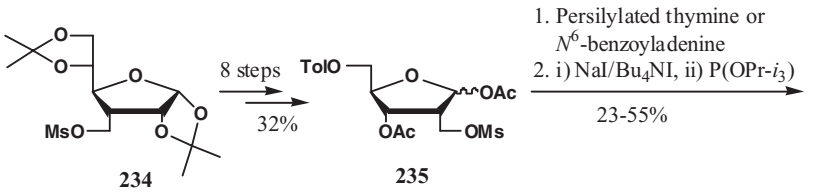
Starting from 3-deoxy-1,2-*O*-isopropylidene-3-*C*-nitromethyl-α-D-allofuranose (**230**) Brink *et al.* prepared 2′-*C*-α-nitromethyluridine (**233b**) as a minor product and its anomer (**233a**) as a major product (*Scheme 75*).[92] Compound **230** was converted to a glycosylating reagent **231** in five steps. Reaction of **231** with *bis*(trimethylsilyl)uracil using tin(IV) chloride as catalyst gave a mixture of anomers **232** in 30% yield. Surprisingly, the reaction gave the stereo-hindered α-isomer predominately (β/α ~1:10). Subsequent removal of the acyl groups with sodium methoxide gave the corresponding nucleoside analogues **233a** and **233b**.

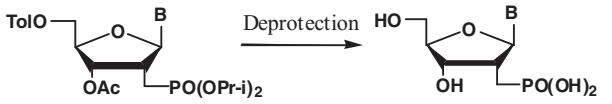


Scheme 75

Similarly, the 2′-*C*-α-(dihydroxyphosphinylmethyl)adenosine (**237a**) and -thymidine (**237b**) were prepared by Mikhailopulo *et al.* starting from a 3-deoxy-3-mesitylmethyl allofuranose (**234**) (*Scheme 76*).[93] Glycosylation of persilylated bases with 2-α-mesitylmethyldeoxyribose (**235**), which was prepared from **234** in eight steps with 32% yield, followed by Arbuzov reaction gave **236a** and **236b** in 23% and 55% yields, respectively. Complete deprotection of **236a** and **236b** gave the corresponding 2′-phosphonates **237a** and **237b** in 58% and 76% yields, respectively.

The phosphoramidites of 2′-deoxy-2′-α-C-methyl and phenyl pyrimidine nucleosides **242a–c** were synthesized by Schmit (*Scheme 77*).[94] Glycosylating agents **239a** and **239b** were prepared from compounds **238a** and **238b**. Glycosylation of persilylated bases (thymine or cytosine) with **239a** and **239b** gave nucleoside derivatives **240a–c** in 68–77% yield with good β-selectivity. Compounds **240a–c** were converted to the 5′-

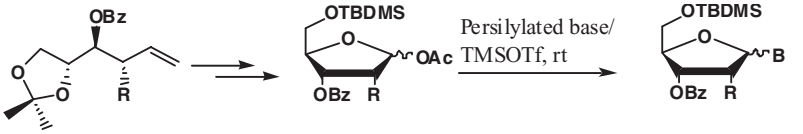




236a: B = A^{Bz}, 23%
236b: B = T, 55%

237a: B = A, 58%
237b: B = T, 76%

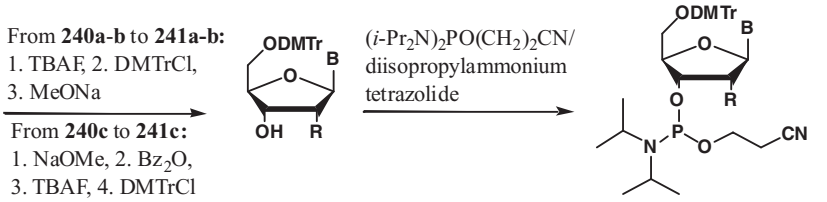
Scheme 76



238a: R = Me
238b: R = Ph

239a: R = Me, 83%
239b: R = Ph, 87%

240a: R = Me, B = T,
β/α = 6.7/1, 77%
240b: R = Ph, B = T,
β/α = 3.5/1, 68%
240c: R = Me, B = C,
β/α = 9/1, 72%



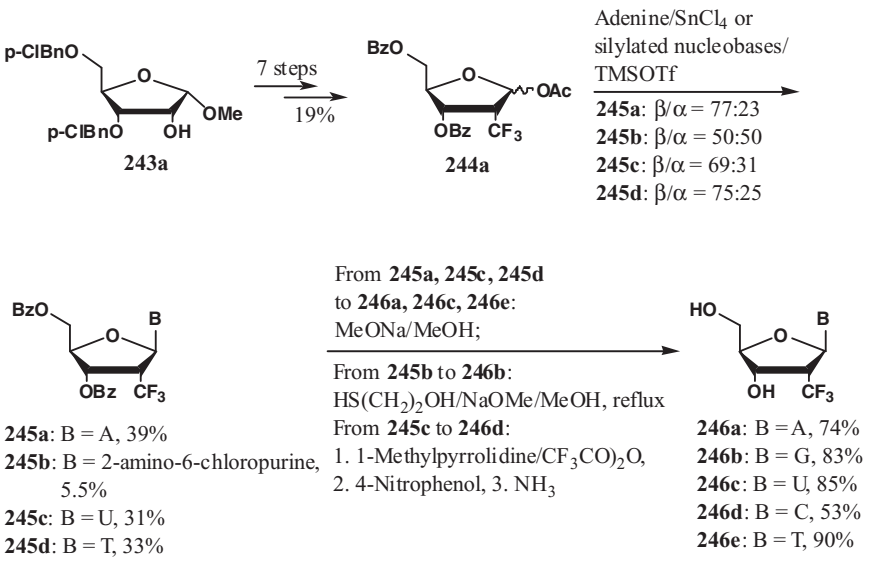
241a: R = Me, B = T, 45%
241b: R = Ph, B = T, 30%
241c: R = Me, B = C^{Bz}, 58%

242a: R = Me, B = T, 85%
242b: R = Ph, B = T, 74%
242c: R = Me, B = C^{Bz}, 83%

Scheme 77

DMTr nucleoside derivatives **241a–c** in 30–58% yields. Phosphitylation of **241a–c** with (*i*-$Pr_2N)_2PO(CH_2)_2CN$ gave the corresponding phosphoramidites **242a–c** in 74–85% yields.

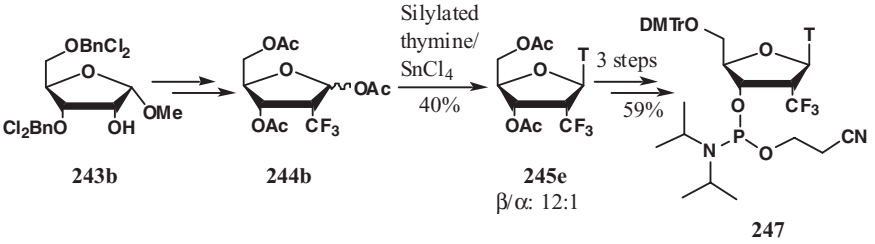
Jeannot *et al.* reported the synthesis of 2′-*C*-α-trifluroromethyldeoxyribonucleosides (**246a–e:** A, G, U, C and T) by glycosylation of adenine or other persilylated nucleobases with 2-α-trifluromethyl-2-deoxyribose derivative **244a** (*Scheme 78*).[95] **244a** was prepared in seven steps, which include oxidation, trifluoromethylation and deoxygenation from methyl 3,5-di-*O*-(4-chlorobenzyl)ribofuranoside (**243a**). Glycoylation of nucleobases with **244a** afforded the corresponding nucleoside derivatives (**245a–d**) in low yield (5.5–39%) and



Scheme 78

low selectivity (β/α ~1:1–3:1). Methanolysis, hydrolysis and aminolysis of **245a–d** gave **246a–e** (A, G, U, C, T) in good yield (53–90%).

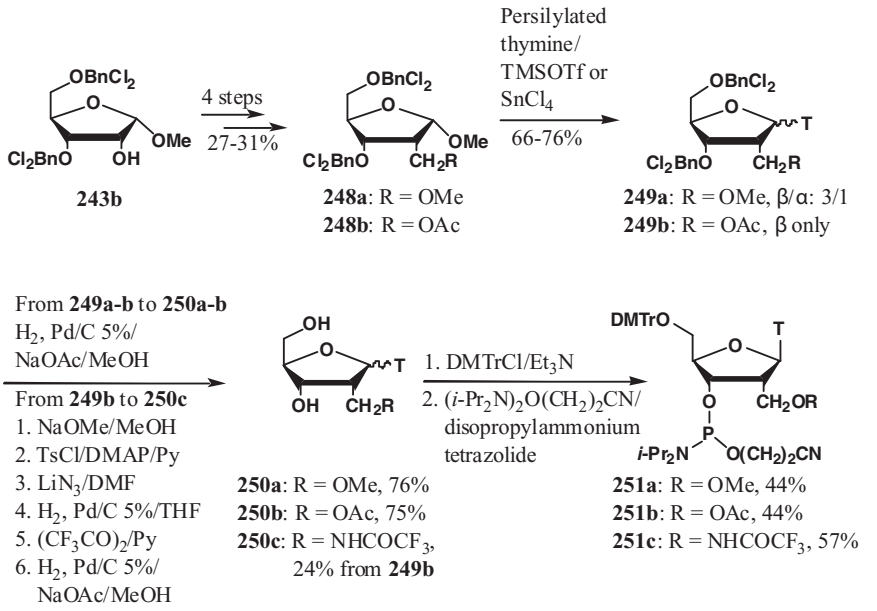
The phosphoramidite derivative of 2′-*C*-α-trifluoromethyl-2′-deoxythymidine (**246e**) was also prepared by Schmit *via* the same reaction sequence starting from 3,5-di-*O*-(2,4-dichlorobenzyl)ribofuranoside **243b** (*Scheme 79*).[96] Glycosylation of bistrimethylsilylthymine with **244b** gave 3′,5′-di-*O*-acetyl-2′-*C*-α-trifluoromethylthymidine **245e** in 40% yield with high β-selectivity (β/α 12:1). However, glycosylation of bistrimethylsilylthymine with **244a** gave 3′,5′-di-*O*-benzoyl-2′-*C*-α-trifluoromethylthymidine **245d** in 33% yield with only 3:1 β/α selectivity (*Scheme 78*).[95] The phosphoramidite **247** was obtained from **245e** in three steps (deprotection, 5′-DMTr protection and phosphitylation) with 59% overall yield.



Scheme 79

3,5-Di-*O*-(2,4-dichlorobenzyl)ribofuranoside **243b** was also used to prepare 2-methoxymethyl ribose derivative (**248a**) and 2-acetoxymethyl ribose derivative (**248b**) in four steps with 27% and 31% overall yields, respectively.[94] Glycosylation of persilylated thymine with **248a** gave 2′-*C*-α-methoxymethylthymidine derivative **249a** in 76% yield with 3:1 β/α selectivity. However, glycosylation with **248b** gave 2′-*C*-α-

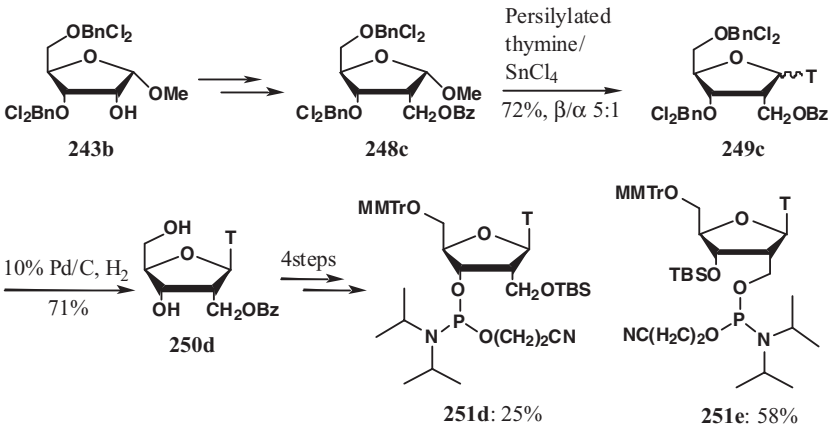
acetoxymethylthymidine derivative **249b** exclusively. The β-selectivity can be explained by anchimeric assistance from the acetyl group analogous to that described for the glycosylation of 2′-acetylated ribose. Debenzylation of **249a** and **249b** with palladium catalyzed hydrogenation gave **250a** and **250b** in 76% and 75% yields, respectively. **248b** was also converted into the 2′-*C*-α-aminomethylthymidine derivative **250c** in six steps with 24% overall yield. 2′-*C*-α-Methoxymethylthymidine (**250a**), 2′-C-α-acetoxymethythymidine (**250b**) and 2′-C-α-trifluoroacetaminomethythymidine **250c** were converted into the corresponding phosphoramidite derivatives **251a–c** in two steps with 44–57% yield (*Scheme 80*).



Scheme 80

Starting from 3,5-di-*O*-(2,4-dichlorobenzyl)ribofuranoside **243b**, Peng *et al.*[97] prepared the benzoyl protected 2-α-hydroxymethylribose (**248c**) as a glycosylation agent using a synthetic strategy analogous to that previously described by Schmit.[94] Coupling of **248c** with bis(trimethylsilyl)thymine in the presence of $SnCl_4$ gave anomeric nucleosides **249c** in good yield with a β/α stereoselectivity of 5:1. It is interesting to note that the glycosylation with the C2-CH_2-OAc derivative gave β-isomer exclusively.[94] However, the acetyl ester was found not to be stable under the conditions used for the subsequent hydrogenolysis reaction. Separation of the anomers by column chromatography was achieved after removal of the 2,4-dichlorobenzyl protecting groups to provide the desired β-anomer **250d** in 71% yield. **250d** was converted to the 2′-CH_2O-phosphoramidite derivative **251e** in four steps with 58% overall yield or 3′-*O*-phosphoramidite derivative **251d** in four steps with 25% overall yield (*Scheme 81*).

Li *et al.* synthesized the phosphoramidite derivatives of 2′-α-methyl-2′-deoxycytidine (**253a**) and 2′-α-hydroxymethyl-2′-deoxycytidine (**253b**) (*Scheme 82*).[98] Methyl 3,5-di-*O*-

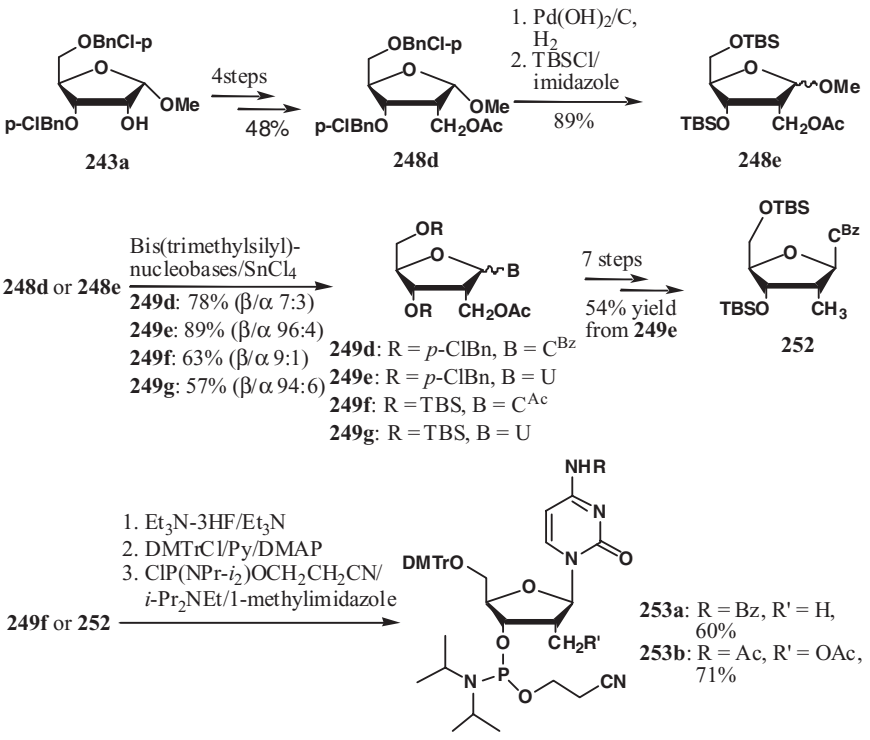


Scheme 81

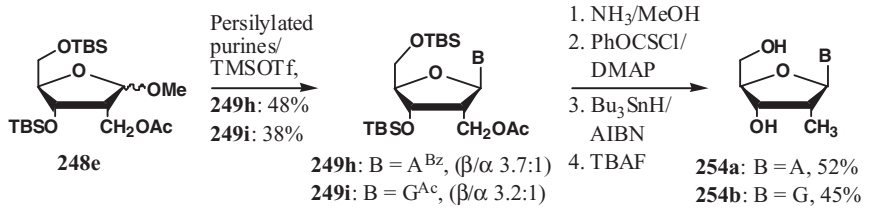
(4-chlorobenzyl)ribofuranoside (**243a**) was converted to methyl 3,5-di-*O*-(4-chlorobenzyl)-2-α-acetoxymethylribofuranoside **248d** in four steps with 48% overall yield.[98] Compound **248d** was then converted to methyl 3,5-di-*O*-TBS-2-α-acetoxymethylribofuranoside (**248e**) in 89% yield.[98] Anomerization of 1-methoxyl group was observed, possibly due to generation of hydrogen chloride during removal of chlorobenzyl group by the catalytic hydrogenation. The glycosylation of pyrimidine nucleobases with **248d** and **248e** gave product **249d–g** in 57–89% yield with β/α selectivity from 7:3 to 24:1. Hydrogenation to remove the chlorobenzyl groups of the cytidine derivative (**249d**) also reduced the cytosine ring. The 2′-α-acetoxymethyluridine derivative **249e** was then converted into 2′-methylcytidine derivative **252** in seven steps with 54% overall yield. The 3′,5′-di-*O*-TBS-cytidine derivatives **252** and **249f** were then converted to the corresponding phosphoramidite derivatives **253a** and **253b** in 60% and 71% yields, respectively.

Glycosylation of persilylated N^6-benzoyladenine and N^2-acetylguanine with methyl 3,5-di-*O*-TBS-2-α-acetoxymethylribofuranoside (**248e**) gave 2′-α-acetoxymethyl adenosine and guanosine derivatrives **249h** and **249i** in 48% and 38% yields, respectively (*Scheme 83*).[99] The β/α selectivity of the glycosylation of purines is ~3.5:1. Compounds **249h** and **249i** were converted into 2′-*C*-α-methyl-2′-deoxyadenosine (**254a**) and 2′-*C*-α-methyl-2′-deoxyguanosine (**254b**) *via* hydrolysis, deoxygenation and desilyation in 52% and 45% overall yields, respectively.

The 2′-*C*-α-monofluoromethylthymidine (**258**) and the corresponding phosphoramidite (**259**) were also synthesized (*Scheme 84*).[96] Methyl 3,5-di-*O*-(2,4-dichlorobenzyl)-2-α-fluoromethylribofuranoside **256,** which was prepared from methyl 3,5-di-*O*-(2,4-dichlorobenzyl)-2-ketoribofuranoside **255** in four steps with 30% overall yield, glycosylated persilylated thymine in the presence of trimethylsilyl triflate to give 2′-fluoromethylthymidine derivative **257** in 76% yield with β/α selectivity ~2.7:1. Removal of dichlorobenzyl groups by hydrogenation gave 2′-*C*-α-monofluoromethylthymidine (**258**) in 87% yield. 5′-DMTr protection, followed by phosphitylation converted **258** to the corresponding 2′-*C*-α-monofluoromethylthymidine **259** in 21% yield.

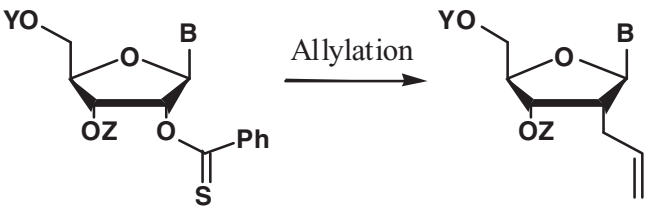


Scheme 82

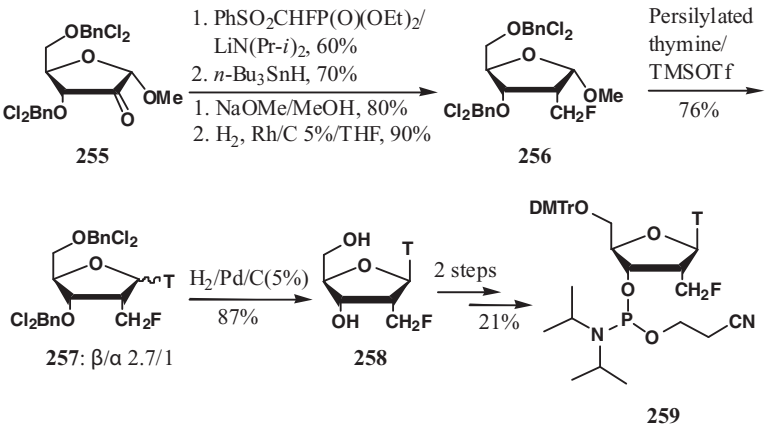


Scheme 83

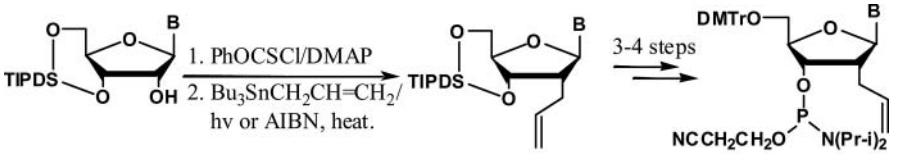
2. *Synthesis* via *2′*-C-*Allylation of the 2′-Thionoesters of Nucleosides*



The 3′,5′-*O*-TIPDS-protected nucleoside derivatives **23** and **260b–f** were converted to 2′-thionoesters, which could react with allyltributyltin irradiated by UV or initiated by AIBN/heat to give the corresponding 2′-*C*-*α*-allylnucleosides **261a–f** in 54–73% yields



Scheme 84



23: B = U
260b: B = T
260c: B = C
260d: B = C^{Ac}
260e: B = A
260f: B = G^{CHNMe2}

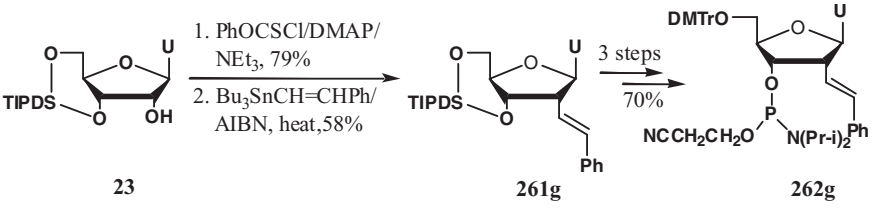
261a: B = U, 65-68%
261b: B = T, 54%
261c: B = C, 58%
261d: B = C^{Ac}, 38%
261e: B = A, 73%
261f: B = G^{CHNMe2}, 62%

262a: B = U, 55-78%
262b: B = T, 65%
262c: B = C^{Bz}, 56%
262d: B = C^{Ac}, 47%
262e: B = A^{Bz}, 62%
262f: B = G^{CHNMe2}, 58%

Scheme 85

(*Scheme 85*).[75, 100–102] The 2′-*C*-allylnucleoside derivatives were converted into the corresponding phosphoramidtes (**262a–f**) in three to four steps (desilylation, DMTr protection and phosphitylation) with 47–78% overall yield.

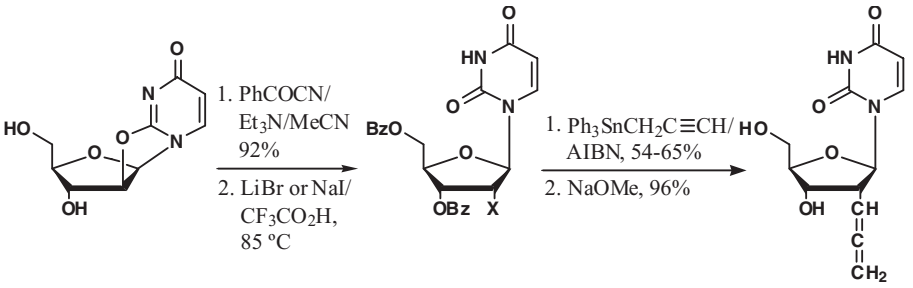
Mesmaeker also reported that 2′-thionoester of 3′,5′-*O*-TIPDS-uridine (**23**) reacted with tributylstyrenyltin in the presence of AIBN to give 2′-*C*-α-(*E*)-styryluridine derivative (**261g**) in 58% yield. Compound **261g** was then converted to 2′-*C*-α-(*E*)-styryluridine phosphoramidite (**262g**) in 32% overall yield from **23** (*Scheme 86*).[101]



23 **261g** **262g**

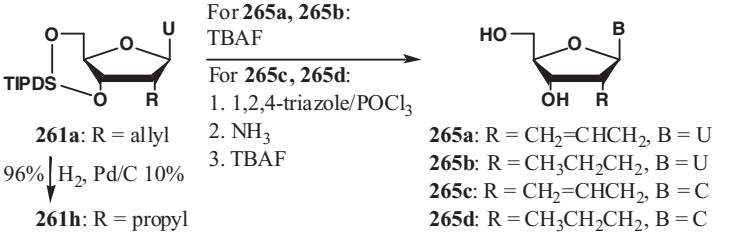
Scheme 86

The 2′-bromouridine uridine derivatives could also be applied to this radical 2′-allylation reaction but the yields are relatively low.[100,103] 2′-*C*-α-Allenyl-2′-deoxyuridine (**264**) could be prepared by the radical reactions of 2′-bromo- (**263a**) or 2′-iodo- (**263b**) uridine derivatives with triphenylpropargyltin in the presence of AIBN in refluxing benzene (*Scheme 87*).[103] In contrast, the *O*-phenylthiocarbonate derivatives are unsatisfactory for this purpose (2′-allenylation) in nucleoside chemistry. The 2′-halouridines (**263a–b**) could be prepared from 2,2′-anhydrouridine in 72–75% yields.



Scheme 87

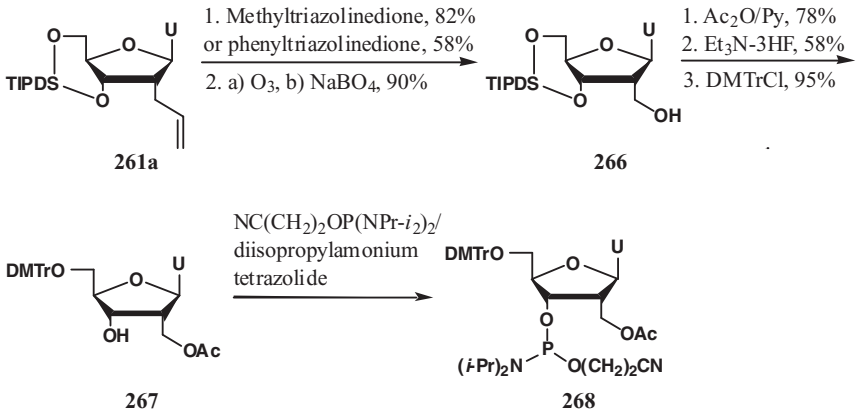
Hydrogenation of 2′-*C*-α-allyluridine derivative **261a** yielded 2′-*C*-α-propyluridine derivative **261h** in 96% yield. 2′-*C*-α-Allyl and 2′-*C*-α-propylnucleosides (**265a–d**) (U and C) could be prepared from **261a** and **261h** accordingly (*Scheme 88*).[75]



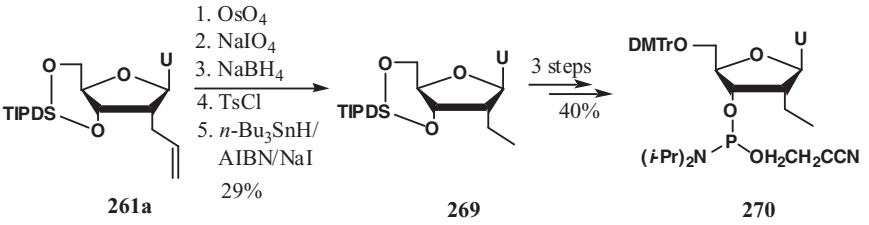
Scheme 88

The 2′-hydroxymethyluridine phosphoramidite derivative (**268**) was obtained starting from 3′,5-*O*-TIPDS-2′-allyluridine (**261a**) by Pavey *et al.*(*Scheme 89*).[104,105] The double bond of the allyl group migrated to form the 2′- alkenyl nucleoside through an ene reaction. Ozone oxidation followed by reduction with $NaBH_4$ gave 2′-hydroxymethyluridine derivative **266** in good yield. Compound **266** could be converted into the 5′-*O*-DMTr-2′-*C*-α-acetoxymethyluridine (**267**) in three steps with 43% overall yield. Phosphitylation of **267** gave the 2′-hydroxymethyluridine phosphoramidite derivative (**268**).

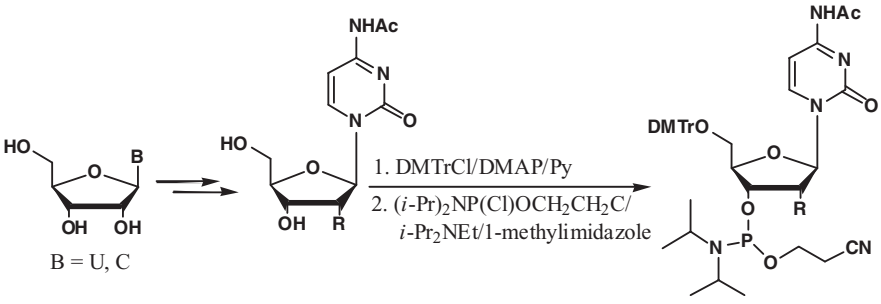
The 2′-*C*-α-ethyluridine phosphoramidite (**270**) was obtained from **261a** *via* eight steps with 11.5% overall yield (*Scheme 90*).[101] Oxidative cleavage of **261a** with osmium tetroxide and sodium periodate, reduction with sodium borohydride, and deoxygenation gave 2′-*C*-α-ethyluridine derivative **269** in 29% yield. **269** was then converted into the corresponding



Scheme 89



Scheme 90



271a: R = $(CH_2)_2OAc$
271b: R = CH_2CH_3
271c: R = $(CH_2)_3OAc$
271d: R = $(CH_2)_2CH_3$
271e: R = $(CH_2)_4OAc$
271f: R = $(CH_2)_3CH_3$

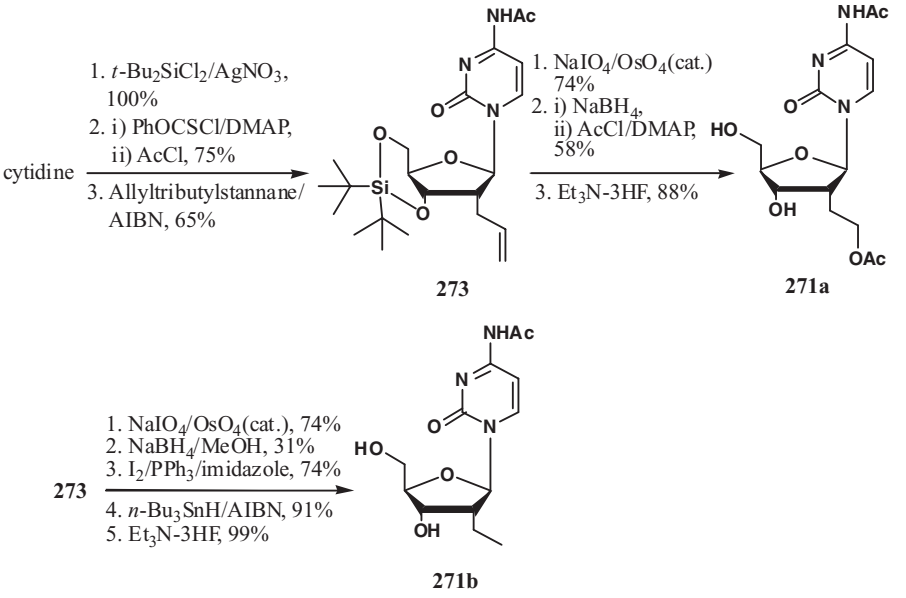
272a: R = $(CH_2)_2OAc$
272b: R = CH_2CH_3
272c: R = $(CH_2)_3OAc$
272d: R = $(CH_2)_2CH_3$
272e: R = $(CH_2)_4OAc$
272f: R = $(CH_2)_3CH_3$

Scheme 91

phosphoramidite derivative **270** in 40% yield *via* desilylation, 5′-DMTr protection and phosphitylation.

A series of 2′-*C*-*α*-(hydroxyalkyl) and 2′-*C*-*α*-alkylcytidine phosphoramidites (**243a–f**) were prepared starting from uridine or cytidine by Li *et al. via* the 2′-*C*-allylation of the 2′-thionoesters of uridine or cytidine derivatives (*Scheme 91*).[106]

The 2′-*C*-α-allyl cytidine derivative **273** could be prepared from cytidine in four steps with 49% overall yield and then converted into the corresponding 2′-*C*-α-acetoxyethylcytidine (**271a**) (38% overall yield) and 2′-*C*-α-ethylcytidine (**271b**) (15% overall yield) *via* oxidative cleavage, reduction, deoxygenation and desilylation (*Scheme 92*).[106]



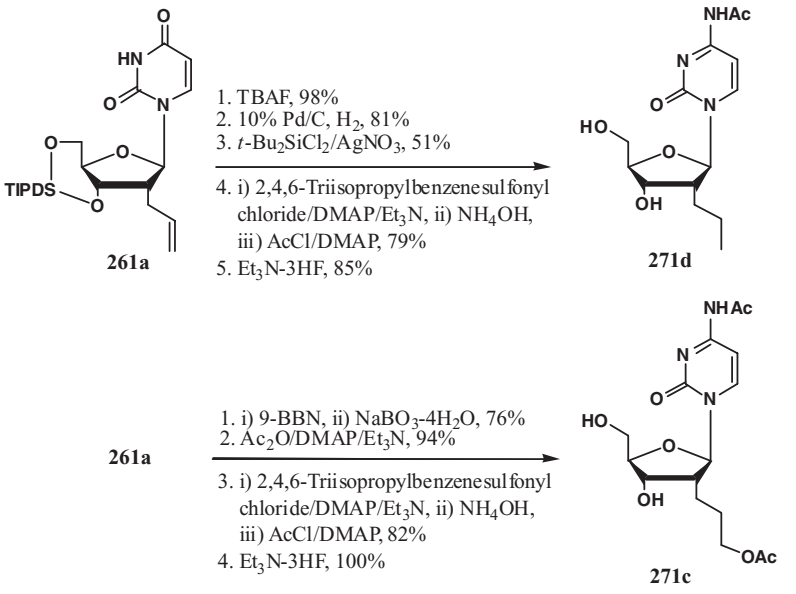
Scheme 92

The 2′-*C*-α-propylcytidine (**271d**) and 2′-*C*-α-acetoxypropylcytidine (**271c**) were prepared from the 2′-*C*-α-allyluridine derivative **261a** in 27% and 59% yields, respectively (*Scheme 93*).[106]

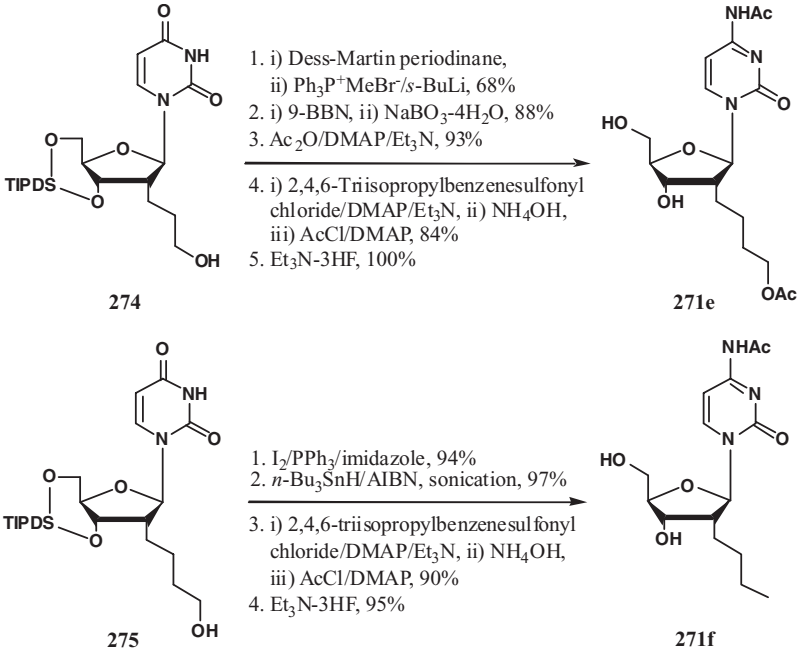
Hydroboration of **261a** with 9-BBN followed by oxidation with sodium perborate yielded the 2′-*C*-α-hydroxypropyluridine derivative **274** in 76% yield. Oxidation of **274** with Dess-Martin periodinane followed by Wittig reaction and hydroboration gave 2′-*C*-α-hydroxybutyluridine derivative **275**, which was further converted into 2′-*C*-α-acetoxybutylcytidine derivative **271e** with 47% overall yield (*Scheme 94*). Deoxygentation of **275** was achieved by iodination with iodine/PPh_3/imidazole followed by deiodonation with tributyltin hydride in the presence of AIBN. Transformation of uridine derivative to cytidine derivative followed by desilylation afforded **271f** from **275** in 78% yield.[106]

The 2′-*C*-α-alkyl or 2′-*C*-α-acetoxyalkylcytidine derivatives **271a–f** were then converted into the corresponding phosphoramidites **272a–f** by 5′-DMTr protection and 3′-phosphitylation (*Scheme 91*).

Starting from 2′-*C*-α-allyluridine derivative **261a**, Lawrence *et al.* synthesized a series of 2′-*C*-α-branched (RCH_2) uridines (**276a–f**) (**a**: R = COOH, **b**: R = $COOCH_2CH = CH_2$, **c**: R = $COOCHPh_2$, **d**: R = $CONH_2$, **e**: R = CH_2OH, **f**: R = CH_2OFpmp, **g**: R = $CH(OH)CH_2OH$, **h**: R = $CH(OAc)CH_2OAc$, **i**: R = CN) (*Scheme 95*).[107–109] Nucleosides **276c**, **276d**, **276f**, and **276h** were converted into the corresponding 2′-*C*-α-branched uridine



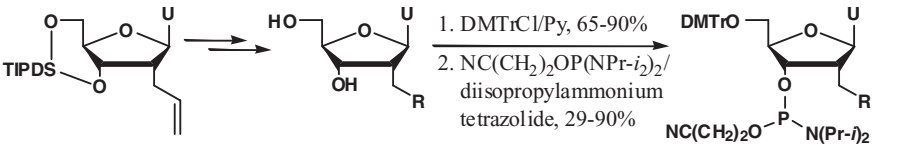
Scheme 93



Scheme 94

phosphoramidites (**277c**, **277d**, **277f**, and **277h**) by 5′-DMTr protection (65–90% yield) and phosphitylation (29–90% yield).

Pedersen *et al.* reported that 2′-*C*-*α*-hydroxyethyl-2′-deoxyuridine derivative **278,** prepared from 2′-*C*-*α*-allyluridine derivative **261a** in three steps with 64% overall

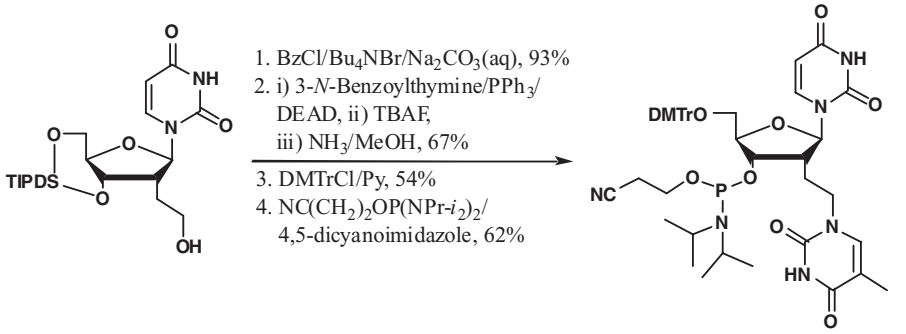


261a

276a: R = COOH
276b: R = $COOCH_2CH{=}CH_2$
276c: R = $COOCHPh_2$
276d: R = $CONH_2$
276e: R = CH_2OH
276f: R = CH_2OFpmp
276g: R = $CH(OH)CH_2OH$
276h: R = $CH(OAc)CH_2OAc$
276i: R = CN

277c: R = $COOCHPh_2$
277d: R = $CONH_2$
277f: R = CH_2OFpmp
277h: R = $CH(OAc)CH_2OAc$

Scheme 95



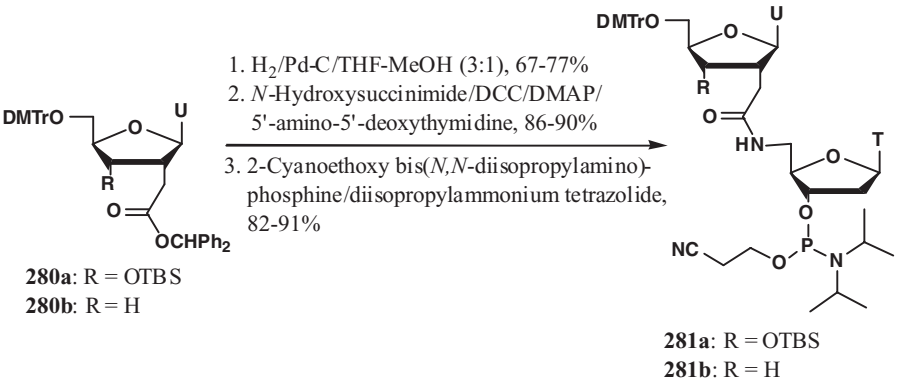
278 **279**

Scheme 96

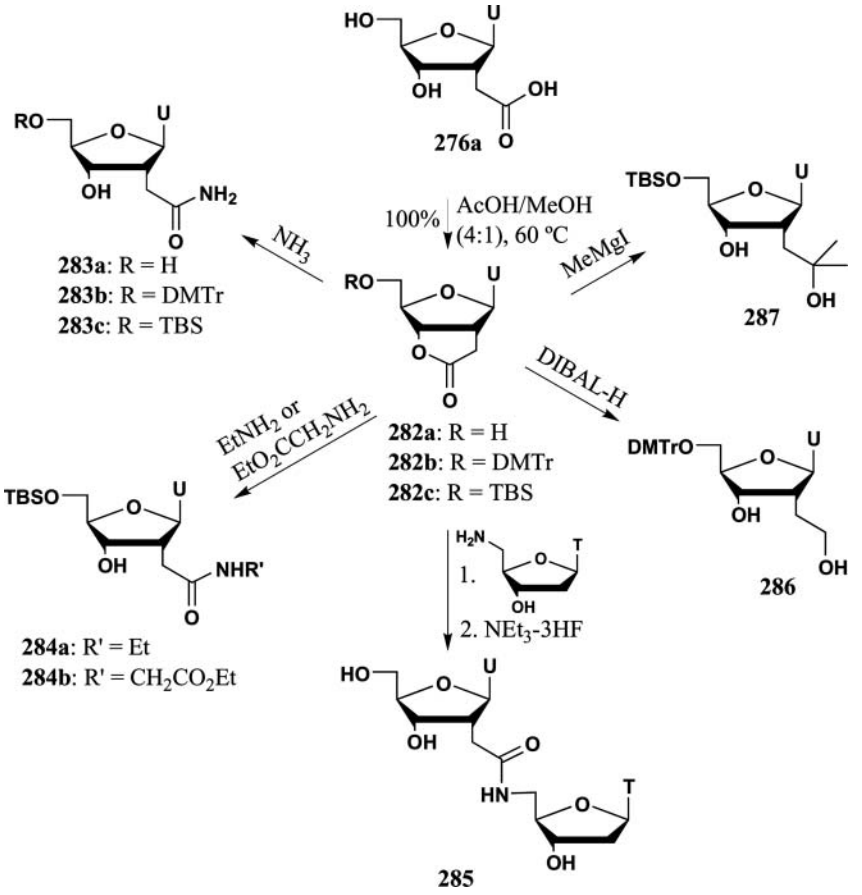
yield, was converted to the phosphoramidite derivative of 2′-deoxy-2′-*C*-(2-(thymine-1-yl)ethyluridine (**279**) in six steps with 21% overall yield (*Scheme 96*).[110]

Chan *et al.* reported the synthesis and incorporation of the phosphoramidite derivatives of 2′,5′-amide linked dinucleotides (*Scheme 97*).[111] The 2′-(diphenylmethoxycarbonyl) methyl-3′-*O*-TBS-2′-deoxyuridine (**280a)** and 2′-(diphenylmethoxycarbonyl)methyl-2′,3′-dideoxyuridine (**280b**) were prepared from **276c** in two to four steps. Removal of the diphenylmethyl group from **280a–b** was achieved by hydrogenolysis to give the carboxylic acids in 67–77% yields. Condensation of the carboxylic acids with 5′-amino-5′-deoxythymidine in the presence of *N*-hydroxysuccinimide/DCC gave the 2′,5′-amide-linked dinucleotides in 86–90% yield. Phosphitylation gave dinucleotide phosphoramidite derivatives **281a** and **281b** in 91% and 82% yields, respectively.

The 2′-*C*-α-carboxymethyluridine (**276a**) was converted to the 2′-*C*-3′-*O*-γ-butyrolactone (**282a**) quantitatively in a mixed solvent system of acetic acid and methanol (80:20) (*Scheme 98*).[108] **282a** as well as its 5′-*O*-DMTr- and 5′-*O*-TBS protected uridine derivatives (**282b–c**) are versatile intermediates for the synthesis of 2′-*C*-branched nucleosides.[112] Aminolysis of **282a–c** with methanolic ammonia gave 2′-α-



Scheme 97

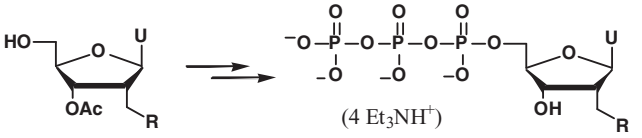


Scheme 98

C-carbamoylmethyl-2′-deoxyuridine derivatives **283a–c** quantitatively. Reaction of **282c** with primary amine (ethylamine, ethyl glycinate or 5′-amino-5′-deoxythymidine) yielded the ethylamide derivative **284a**, the glycinyl derivative **284b** and the 2′,5′-amide-linked dinucleotide derivative **285.** Reduction of **282b** with DIBAL-H gave 2′-hydroxyethyluridine

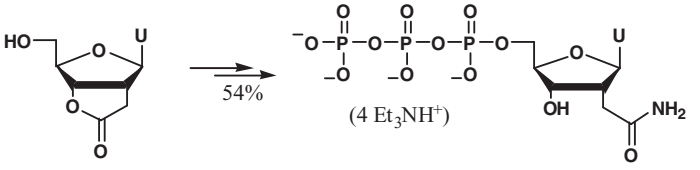
286 in 70% yield. Reaction of **282c** with methylmagnesium iodide gave the 2′-(2-hydroxy-2-methylpropyl)uridine derivative (**287**) in 50% yield.

The 5′-triphosphates of 2′-*C*-α-hydroxymethyluridne (**289a**), 2′-*C*-α-hydroxyethyluridine (**289b**) and 2′-*C*-α-carbamoylmethyluridnes (**289c**) were synthesized from the corresponding acetyl-protected nucleosides **288a, 288b** and uridine 2′-*C*-3′-*O*-γ-butyrolactone **282a** (*Scheme 99*).[113] Compounds **288a**, **288b** and **282a** were prepared from 2′-*C*-α-allyl-2′-deoxyuridine derivative (**261a**). The 5′-triphosphate nucleoside **289a** was found to be a substrate for T7 RNA polymerase but **289b** and **289c** were not substrates for the enzyme.



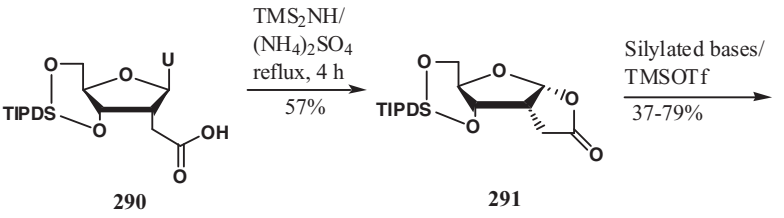
288a: R = OAc
288b: R = CH_2OAc

289a: R = OH,47%
289b: R = CH_2OH, 56%

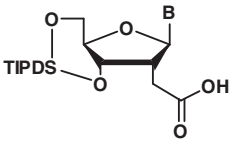


282a **289c**

Scheme 99



290 **291**



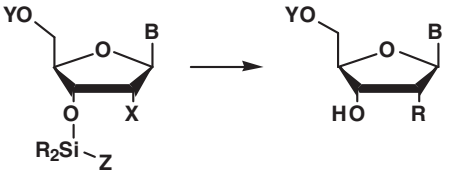
292a: B = T, 79%
292b: B = 5-Bromouracil, 69%
292c:B = 5-Fluorouracil, 47%
292d: B = N^4-Benzoylcytosine, 58%
292e: B = 2,6-Dichloropurine, 62%
292f: B = Adenine, 37%

Scheme 100

Fehring *et al.* reported that 2′-carboxymethyluridine derivative **290** could be used to prepare a series of 2′-carboxymethyl nucleosides **292a–f** (*Scheme 100*).[114,115] Treatment of **290** with HMDS gave the 1,2-lactone **291** in 57% yield. Glycosylation of various

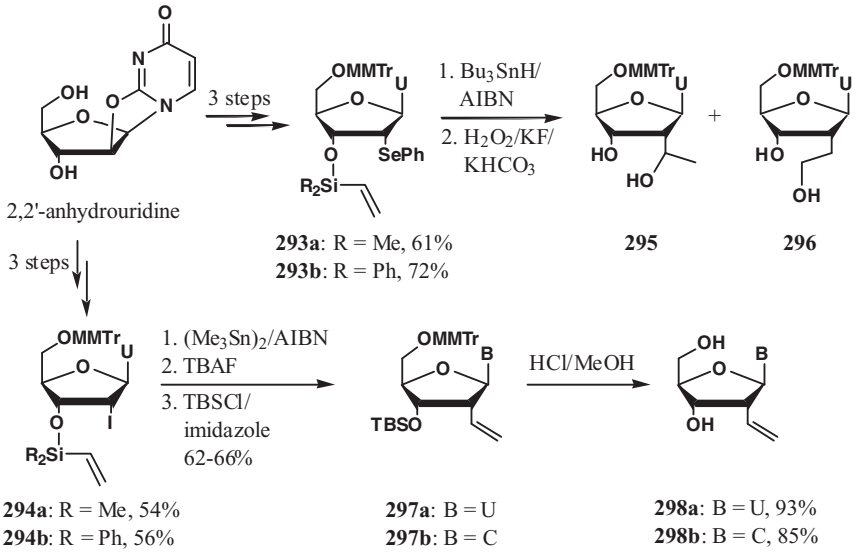
persilylated nucleobases with lactone **291** in the presence of trimethylsilyl triflate gave 2′-carboxymethyl nucleosides: **292a–f** in 37–79% yields.

3. Synthesis via *Radical Cyclization Reaction of 3′-*O*-Unsaturated Silyl Nucleoside Derivatives*



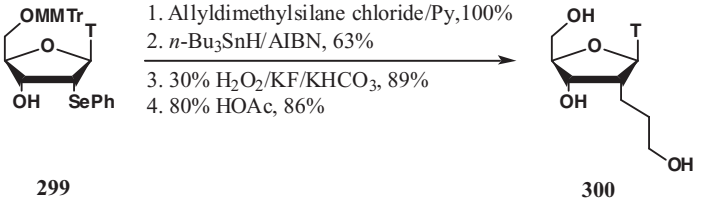
Z: vinyl, allyl, alkynyl

Sukeda *et al.* reported that the 2′-phenylseleno-3′-*O*-vinylsilyl-2′-deoxyuridines (**293a** and **293b**) and 2′-iodo-3′-*O*-vinylsilyl-2′-deoxyuridines (**294a** and **294b**) could be prepared from 2,2′-anhydrouridine in three steps with 54–72% yields (*Scheme 101*).[116] The radical reactions of the 2′-*C*-phenylselenouridine derivatives **293a** and **293b** were performed under reductive conditions with Bu_3SnH and AIBN in refluxing benzene, and the products were purified after the oxidation. If the reaction was carried out by heating the mixture of **293a** or **293b** with Bu_3SnH/AIBN in benzene under reflux for one hour, the 2′-(1-hydroxyethyl)uridine derivative **295** was obtained predominately. However, if the same reaction was carried out by adding a mixture of Bu_3SnH and AIBN in benzene slowly over 4 h to a refluxing solution of **293a** or **293b** in benzene, 2′-(2-hydroxyethyl)uridine derivative **296** was generated predominately.



Scheme 101

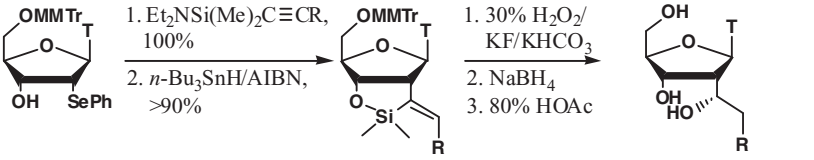
When the 2′-iodo substrates (**294a** or **294b**) were heated under reflux with $(Me_3Sn)_2$ and AIBN in benzene, the radical atom-transfer reaction proceeded, and the 2′-vinyl derivative **297a** was obtained in 62–66% yield after treatment of the radical reaction product with TBAF followed by TBSCl/imidazole (*Scheme 101*).[116] The 2′-deoxy-2′-*C*-vinyluridine derivative **297a** was treated with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl)/DMAP in acetonitrile followed by ammonolysis to give the corresponding cytidine derivative **297b** in 93% yield. Removal of the hydroxyl-protecting groups of **297a** and **297b** with hydrogen chloride in methanol afforded the 2′-deoxy-2′-*C*-vinyluridine (**298a**) and –cytidine (**298b**) in 93% and 85% yields, respectively.



299 **300**

Scheme 102

Xi *et al.* reported the synthesis of 2′-*C*-α-(3-hydroxypropyl)thymidine (**300**) from 2′-phenylseleno-5′-*O*-MMTr-thymidine (**299**) in four steps with 48% overall yield (*Scheme 102*).[117] The 3′-hydroxyl group of 2′-phenylseleno-5′-*O*-MMTr-thymidine (**277**) was silylated quantitatively with allylydimethylsilane chloride. Radical cyclization of the 3′-*O*-allyldimethylsilyl-2′-phenylseleno-thymidine with *n*-Bu_3SnH and AIBN followed by oxidation and removal of 5′-*O*-MMTr group generated 2′-*C*-α-(3-hydroxypropyl)thymidine (**300**).



299

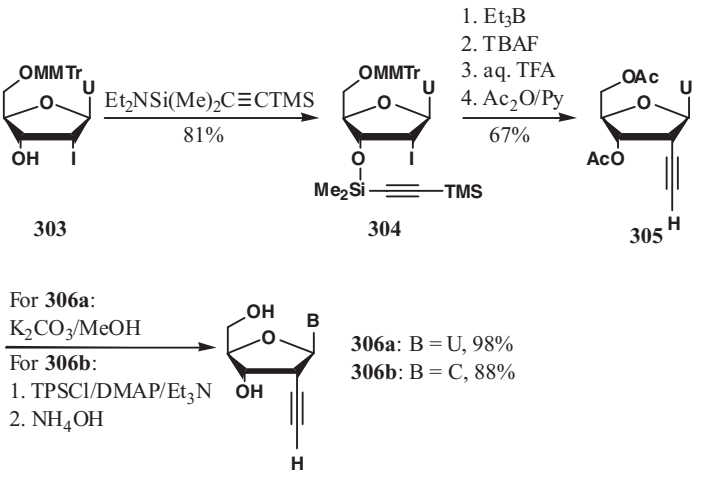
301a: R = Ph
301b: R = TMS
301c: R = CH_2OTBS

302a: R = Ph, 35%
302b: R = H, 12%
302c: R = CH_2OH, 28%

Scheme 103

Xi *et al.* also reported that the radical cyclization of 3′-*O*-alkynyldimethylsilyl-2′-phenylseleno-thymidine derivative with Bu_3SnH and AIBN gave **301a–c** in > 90% yield (*Scheme 103*).[118] Oxidation of **301a–c** gave the 2′-carbonylthymidine derivative; reduction with sodium borohydride followed by the removal of MMTr group gave 2′-*C*-α-(1-hydroxyalkyl)thymidine **302a–c** (three steps, 12–35% overall yields).

Sukeda *et al.* carried out the radical cyclization reaction of 3′-*O*-dimethyl(trimethylsilylethynyl)silyl-2′-iodouridine derivative (**304**) initiated with Et_3B (*Scheme 104*).[119,120] The reaction gave 3′,5′-di-*O*-acetyl-2′-*C*-α-ethynyluridine (**305**) in 67% yield after desilylation with TBAF, removal of MMTr group with trifluoroacetic acid, and acetylation with acetic anhydride. The 2′-deoxy-2′-*C*-ethynyluridine (**306a**) and



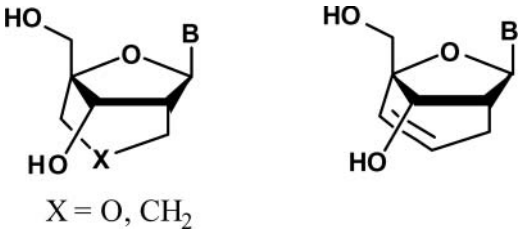
Scheme 104

–cytidine (**306b**) nucleosides were then prepared from **305** in 98% and 88% yields, respectively.

V. Conformationally Locked 2′-Branched Nucleosides

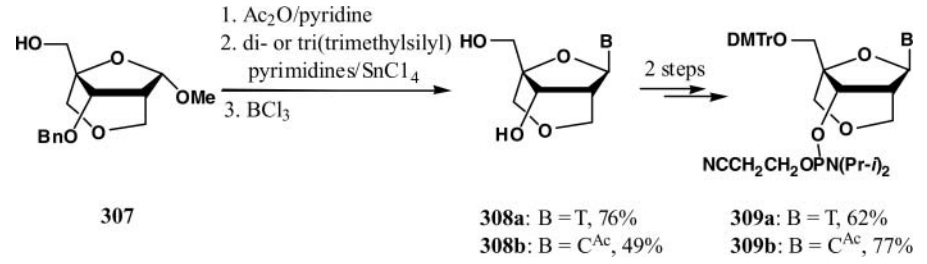
1. 2′-C-Bicyclic Nucleosides

a) 2′,4′-C-Bridged Nucleosides



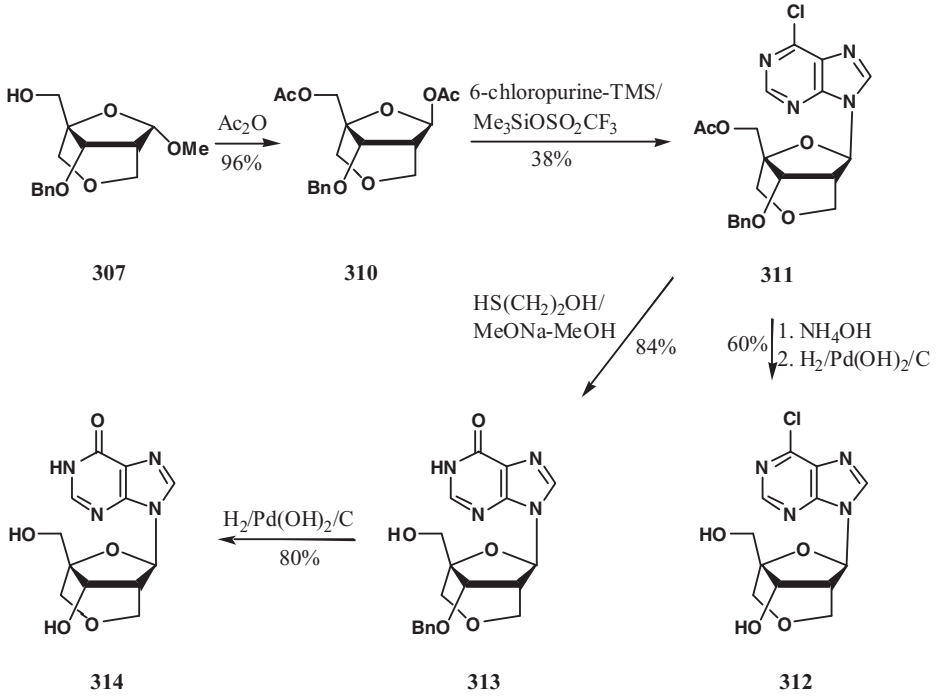
Wang *et al.*[121] reported the synthesis of 2′,4′-*C*-bridged bicyclonucleosides (**308**) and their phosphoramidites (**309**) starting from 2′,4′-*C*-bridged-2′-deoxyribofuranoside (**307**)[122] (*Scheme 105*). Protection of **307** with an acetyl group (Ac_2O/pyridine), followed by condensation with the silylated thymine or N^4-acetylcytosine in the presence of $SnCl_4$ and subsequent deprotection with BCl_3, afforded 2′,4′-*C*-bridged bicyclonucleosides **308a** (76% yield) and **308b** (49% yield), respectively. Compounds **308a** and **308b** were then converted to the corresponding phosphoramidites **309a** and **309b** in good yields. These phosphoramidites were subsequently incorporated into oligodeoxynucleotides. Hybridization studies have shown that these bicyclonucleosides hybridize to the complementary RNA significantly more strongly than do the corresponding oligodeoxynucleotides.

In the absence of base, reaction of **307** with acetic anhydride yielded **310** in 96% yield (*Scheme 106*). Glycosylation of silylated 6-chloropurine with **310** afforded **311** in 38%



307 **308a**: B = T, 76% **309a**: B = T, 62%
308b: B = C^{Ac}, 49% **309b**: B = C^{Ac}, 77%

Scheme 105



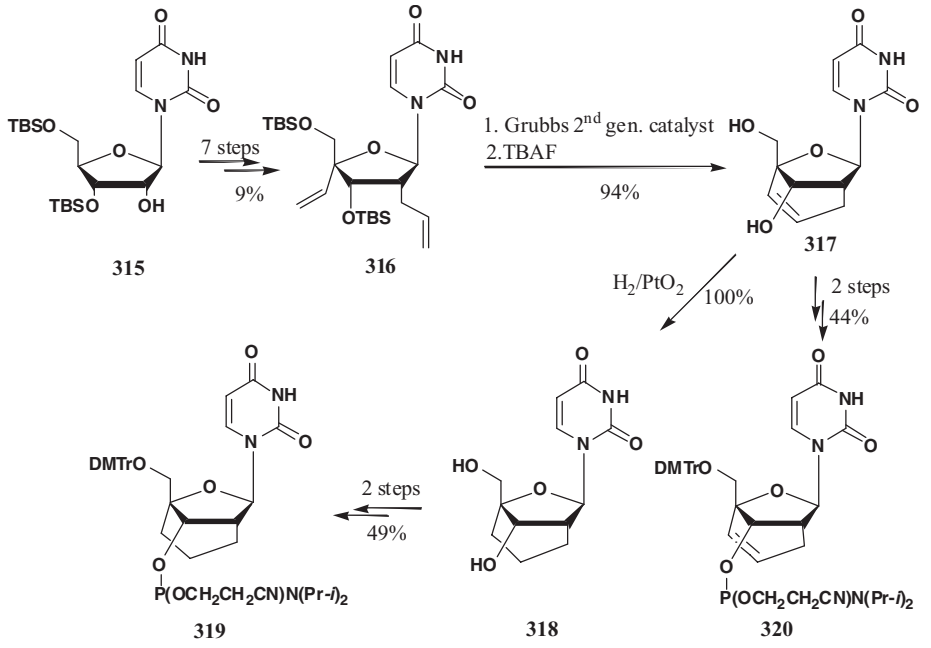
307 **310** **311**

314 **313** **312**

Scheme 106

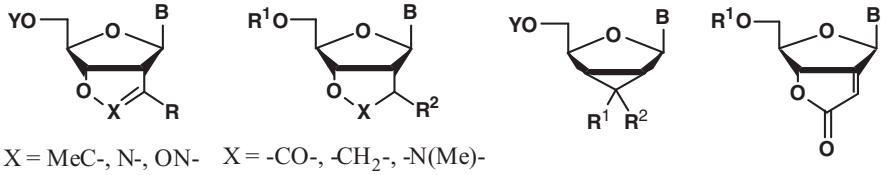
yield. Deprotection of **311** with ammonia followed by debenzylation with $Pd(OH)_2$-C/H_2 gave the bicyclic nucleoside **312** in 60% yield. Treatment of **311** with mercaptoethanol in the presence of base followed by debenzylation gave the bicyclic nucleoside **314** in 67% yield.[123]

Recently, Albaex *et al.*[124] synthesized two bicyclic 2′-deoxynucleoside analogues containing a saturated (**319**) and an unsaturated (**320**) three-carbon 2′,4′-linkage using a ring-closing metathesis-based linear strategy starting from 3′,5′-di-*O*-TBS-protected uridine (**315**, *Scheme 107*). The key-step, ring-closure *via* a ring-closing metathesis (RCM) reaction, gives an excellent yield using Grubbs' second-generation catalyst.



Scheme 107

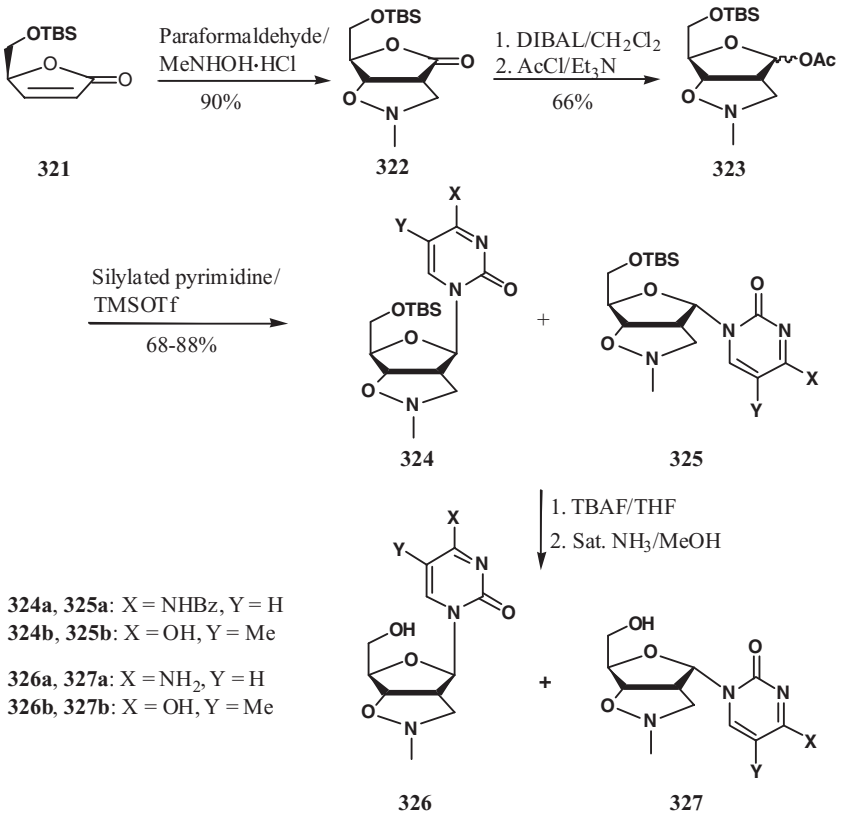
b) 2′,3′-C-Bridged Nucleosides



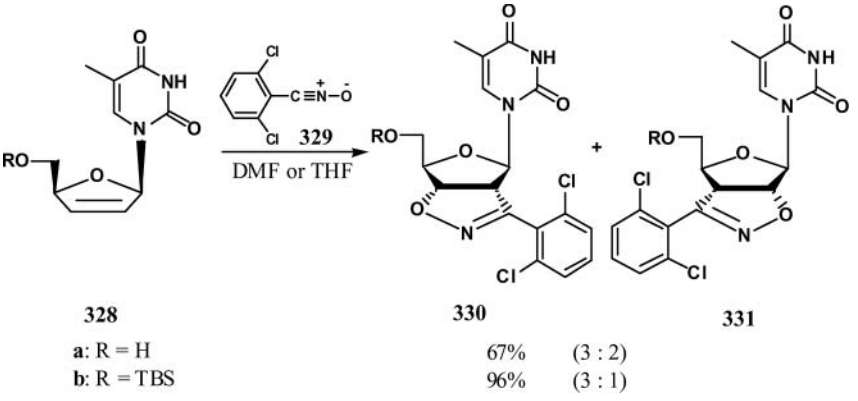
X = MeC-, N-, ON- X = -CO-, -CH_2-, -N(Me)-

Xiang *et al.*[125] prepared [3,3,0] bicyclic isoxazolidinyl cytidine (**326a**) and thymidine (**326b**) from α,β-unsaturated γ-lactone (**321**) (*Scheme 108*). Treatment of **321** with $(CH_2O)_n$ and MeNHOH under refluxing conditions gave the cycloaddition product **322** in good yield. Reduction of **322** by DIBAL followed by acetylation provided **323**. Glycosylation of silylated N^4-benzoylcytosine or thymidine with **323** gave the nucleoside derivatives **324** and **325**. The α:β ratio of the condensed products depends on the solvent: methylene chloride gave a higher α:β ratio (**325a**:**324a**, 4:1; **325b**:**324b**, 3:1) than acetonitrile (**325a**:**324a**, 5:3; **325b**:**324b**, 3:2). After deprotection by TBAF and NH_3 in MeOH, the [3,3,0] bicyclic isoxazolidinyl cytidines (**326a** and **327a**) were obtained in 94% and 97% yields, respectively.

Kim *et al.*[126] reported that a 1,3-dipolar cycloaddition reaction of 2,6-dichlorobenzonitrile oxide (**329**) with the unsaturated furanose moiety of 2′,3′-didehydro-2′,3′-dideoxythymidine (**328**) in DMF afforded a mixture of regioisomeric cycloaddition products **330** and **331** in good yields. The major isomer **330** can be isolated by flash chromatography (*Scheme 109*).

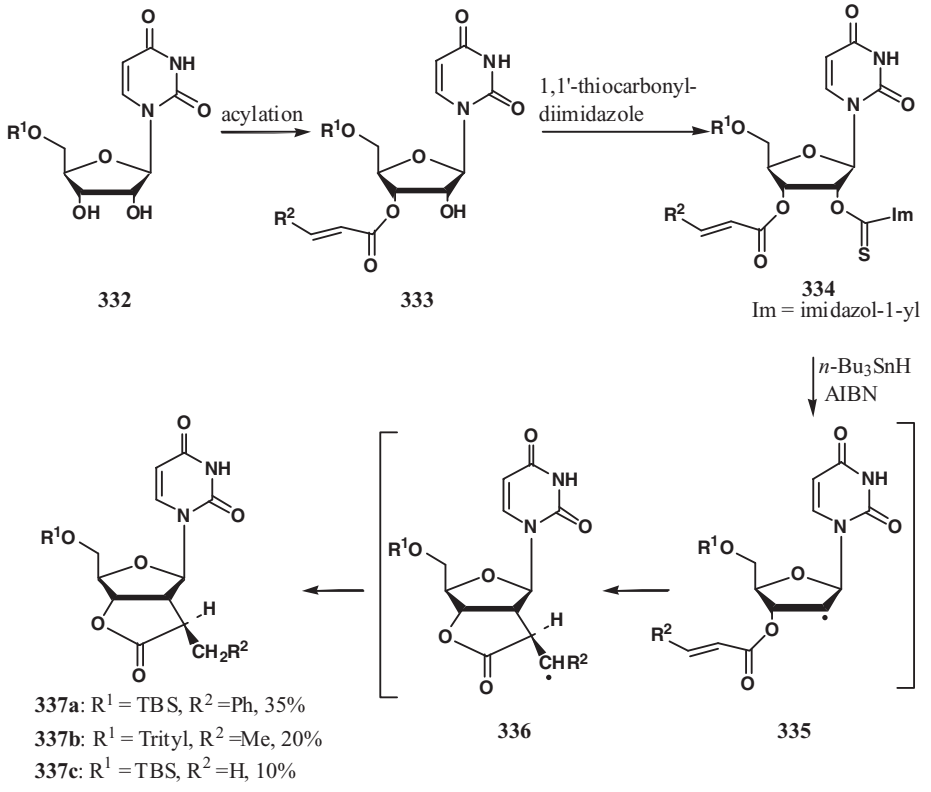


Scheme 108



Scheme 109

Velazquez *et al.*[127] reported the synthesis of fused [3,3,0] lactones of nucleosides **337a–c** by intramolecular addition of C-2′ radicals to the α-position of α:β-unsaturated esters using tributyltin hydride and azobisisobutyronitrile (AIBN) (*Scheme 110*). The protected nucleoside derivative **332** undergoes acylation by reaction with the corresponding α:β-unsaturated acid or acid chloride to give the α:β-unsaturated ester **333**. Reaction of

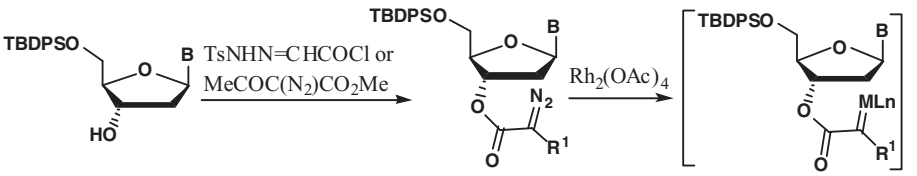


Scheme 110

333 with 1,l′-thiocarbonyldiimidazole affords the intermediate **334**. Treatment of **334** with *n*-Bu_3SnH/AIBN gave the cyclized nucleosides **337a–c** in 10–35% yields.

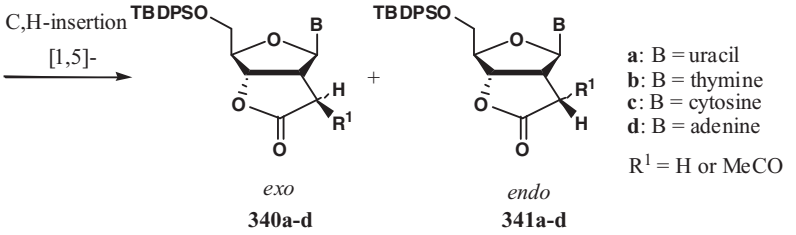
In 2000, Lim *et al.*[128] reported a new stereoselective synthesis of α-substituted-γ-butyrolactones of nucleosides **340a–d** and **341a–d** (58–80% yield) with high diastereoselectivities (*exo*:*endo* 95:5∼98:2) *via* [1,5]-C,H insertion reactions of the 3′-α-diazoacetates of nucleosides **338a–d** (*Scheme 111*). Transesterification of **338a–d**, followed by diazo transfer with methanesulfonyl azide and triethylamine in acetonitrile afforded 3′-α-diazoester derivatives (**339a–d**). C,H-insertion of 2′-deoxy-3′-α-diazoacetates of nucleosides **339a–d** were performed in the presence of dirhodium tetraacetate (1.0 mol%) in dichloromethane at room temperature. In addition, (*E*)-2′-deoxy-2′-(carboxymethylene)-5′-*O*-trityluridine-3′,2′-γ-lactone (**345**), a chiral synthon in the synthesis of 2′-*C*-branched nucleosides, was prepared in 45% overall yield starting from compound **342** using this 1,5-C,H insertion (*Scheme 112*).

Wu *et al.*[129] described a new general approach for the synthesis of the five-membered 2′-deoxy-2′,3′-ribo-fused furano derivative **350** and the 2′,3′-dideoxy-2′,3′-ribo-cyclopropane derivatives **351a,b** through the Michael addition reactions of α,β-ene-3′-phenylselenone **349** with active methylene compounds (*Scheme 113*). Treatment of **346** with PhSeSePh in the presence of $LiAlH_4$ and mesylation of the 2′-OH using methanesulfonyl chloride gave compound **347** in 49% yield. Elimination of the 2′-*O*-mesylate of **347** with *t*-BuOK gave



338a: B = uracil
338b: B = thymine
338c: B = cytosine
338d: B = adenine

339a: B = uracil
339b: B = thymine
339c: B = cytosine
339d: B = adenine



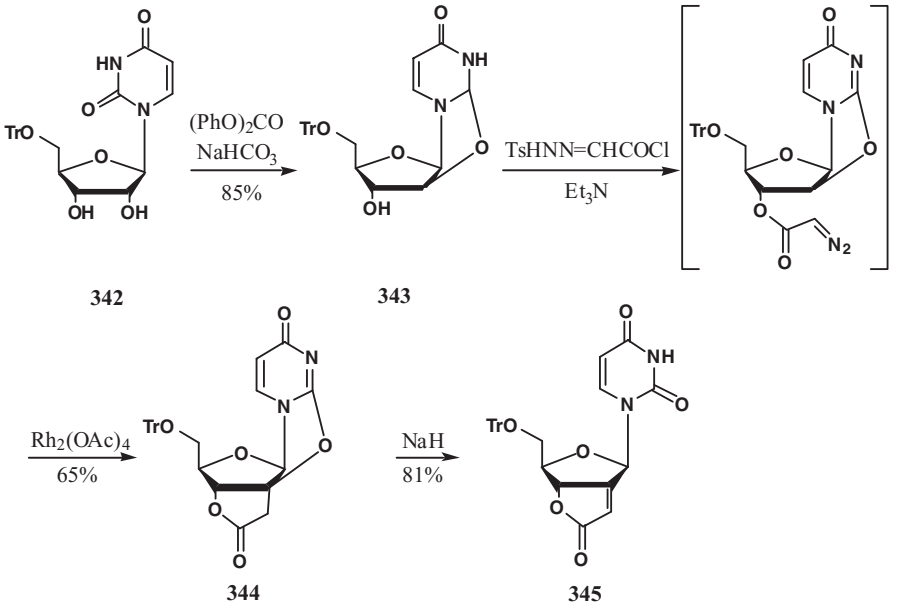
exo
340a-d

endo
341a-d

a: B = uracil
b: B = thymine
c: B = cytosine
d: B = adenine

R^1 = H or MeCO

Scheme 111

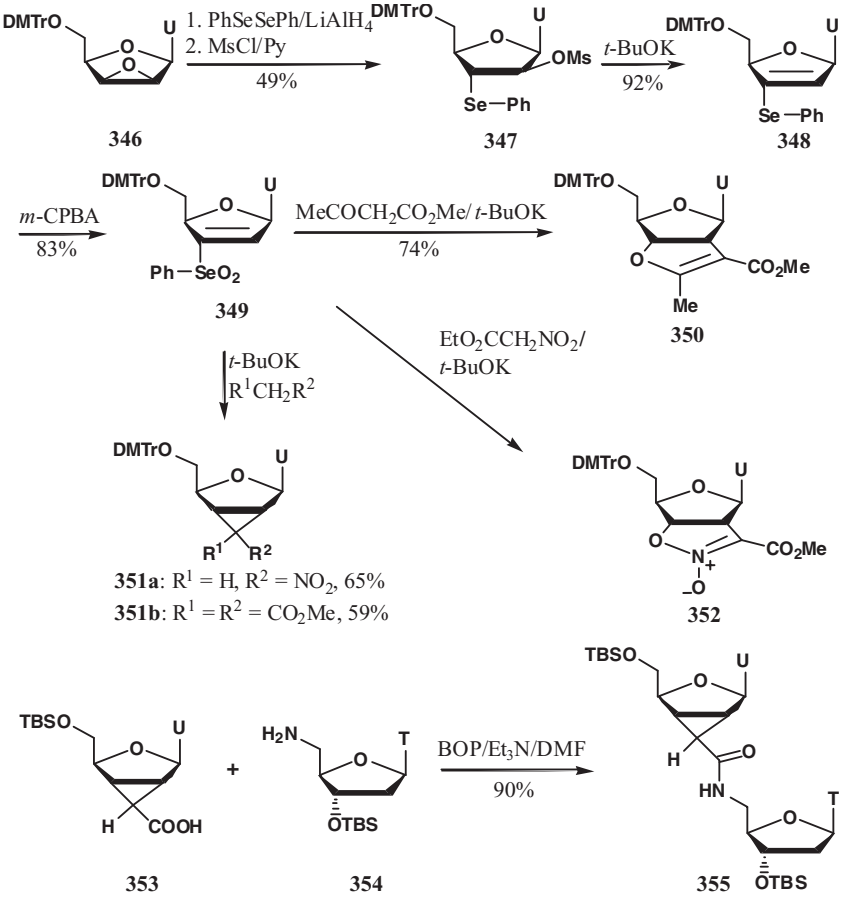


342 **343**

344 **345**

Scheme 112

α,β-ene-3′-phenylselenide **348**, which was subsequently oxidized by *m*-chloroperbenzoic acid to give α,β-ene-3′-phenyl-selenone **349** in 83% yield. Compounds **350** and **351** were obtained in good yield by treatment of **349** with active methylene compounds. Using the same conditions, Yannopulous *et al.*[130] prepared compounds **352** and **353**. Reaction of **353**

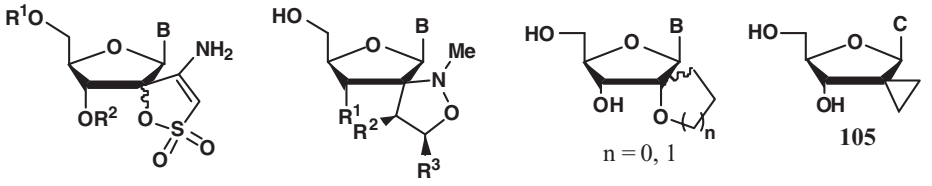


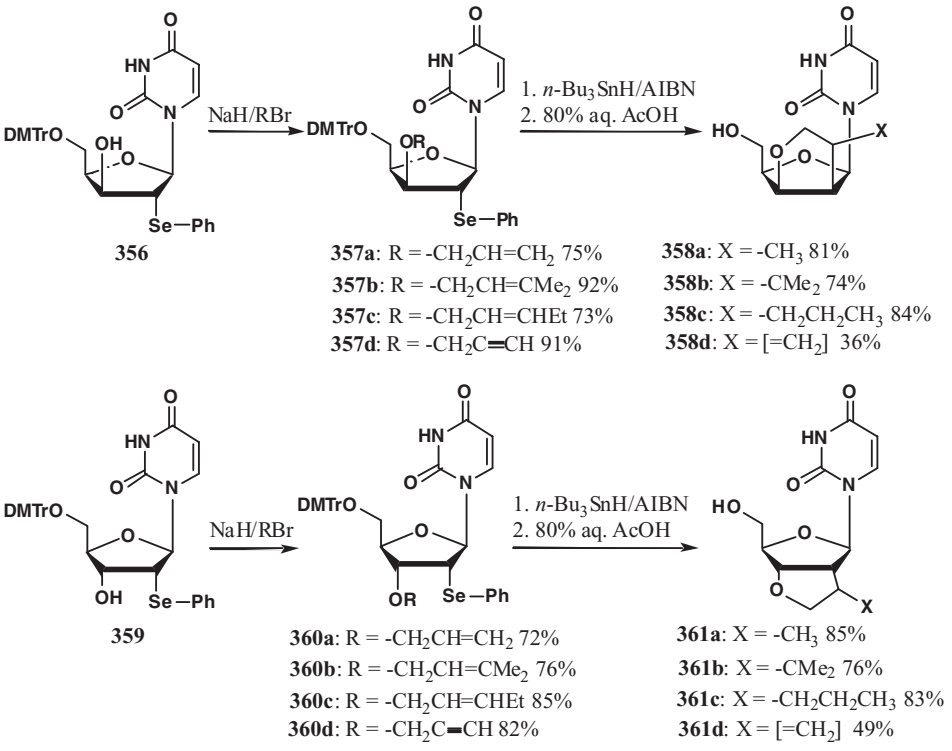
Scheme 113

with 5′-amino-5′-deoxythymidine (**354**) using BOP as the condensing agent gave the dimer **355** in 90% yield.

Compounds **356** and **357** were alkylated with various allyl- or propargyl bromides in the presence of sodium hydride at room temperature to give the corresponding 2′-phenylseleno-3′-*O*-ally1 ethers **357** and **360** in good yields.[131] Radical cyclization of **357** and **360** with Bu_3SnH/AIBN, followed by deprotection with 80% aq. AcOH, gave exclusively 5-*exo* ring-closure α- and β-face nucleosides **358** and **361** (*Scheme 114*).

2. Synthesis of 2′-C-Spiro Nucleosides

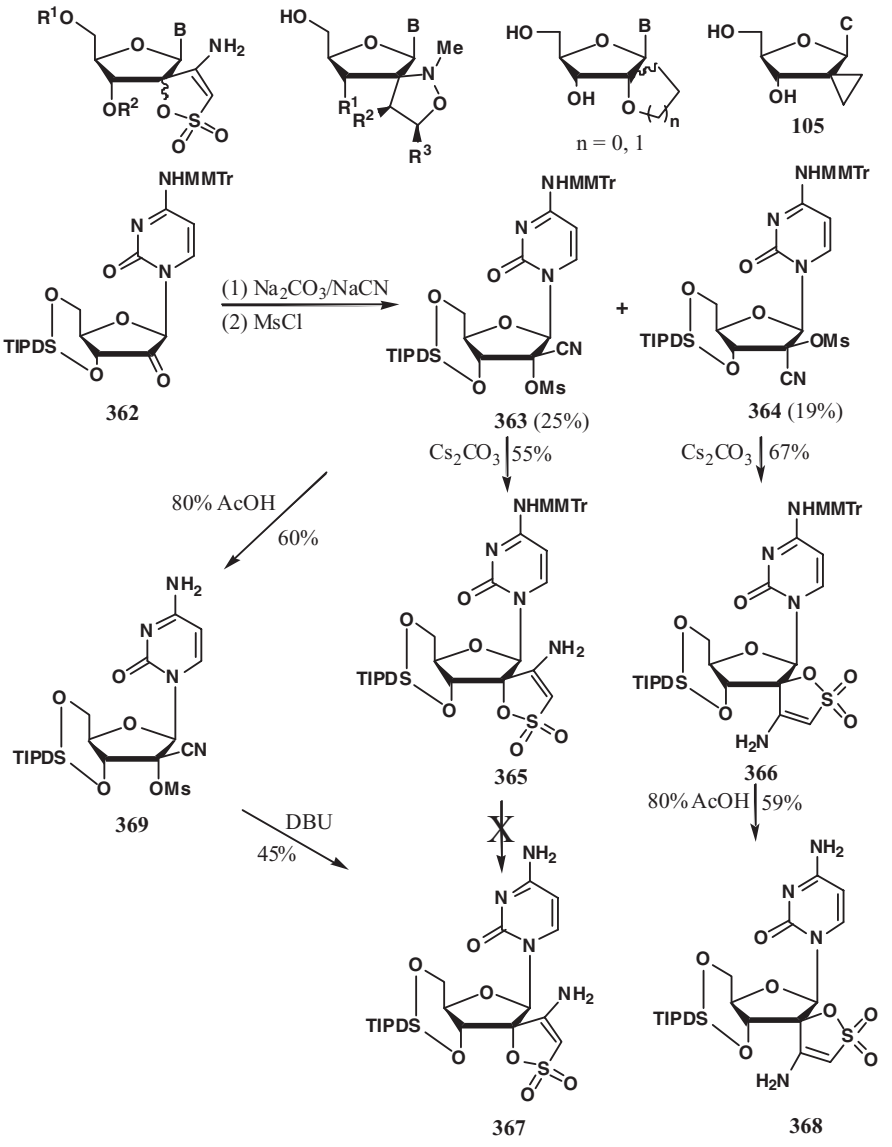




Scheme 114

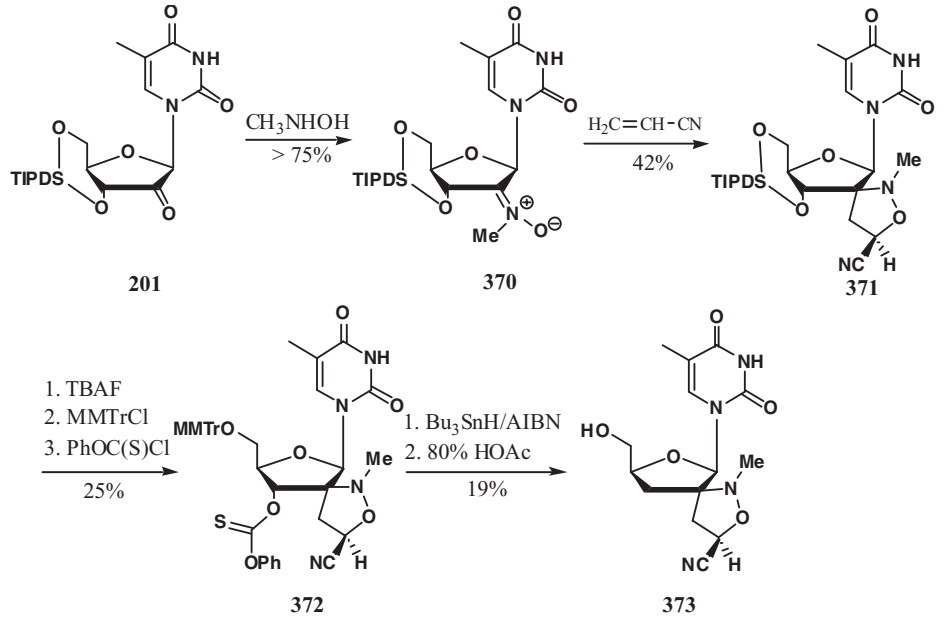
2′-Deoxy-2′-spirocyclopropyl cytidine (**105**) was synthesized by Czernecki *et al.* and shown in *Scheme 35*. Velazquez *et al.*[132] synthesized 2′-spiro ribonucleoside **367** and 2′-spiro arabinonucleosides **368** from 2′-ketonucleoside **362** (*Scheme 115*). Reaction of **362** with sodium cyanide, followed by protection of the 2′-OH with mesyl chloride, afforded two nucleoside 2′-cyanohydrins **363** (25% yield) and **364** (19% yield). Reaction of **363** and **364** with Cs_2CO_3 afforded 2′-spiro derivatives **365** (55% yield) and **366** (67% yield). Deprotection of 2′-spiro arabinonucleoside **366** with 80% AcOH gave the *N*-deprotected spiro nucleoside (**368**) in 59% yield. However, a similar attempt at deprotection of the ribo-spironucleoside **365** did not give the corresponding nucleoside **367**. Compound **367** was obtained in 45% yield by a different synthetic strategy, which consisted of *N*-deprotection of cyanomesylate **363** with 80% acetic acid to give cyanomesylate **369**, followed by treatment of **369** with DBU to effect ring closure.

Hossain *et al.*[133] reported the synthesis of a new class of 2′-spiro nucleosides (**373** and **376**) by 1,3-dipolar cycloaddition reactions of nucleoside *C*-alkenyl nitrones **370** and **374**. Compound **201** was treated with *N*-methylhydroxylamine hydrochloride in pyridine solution to give the corresponding 2′-(*Z*)-methylnitrone **370** in 75% yield. Methylnitrone **370** was treated with acrylonitrile to give **371**. After desilylation with TBAF, 5′-MMTr protection and 3′-deoxygenation, 3′-deoxy-2′-spiro nucleoside **373** was obtained from **371** in 5% yield (*Scheme 116*). Similarly, 2′-spiro nucleoside **376** was obtained in 32% yield from methylnitrone **374** (*Scheme 117*).[134]

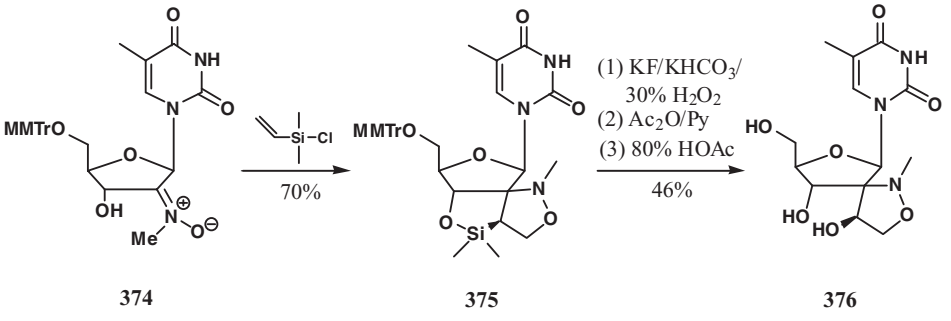


Scheme 115

Recently Wengel *et al.*[135] reported the synthesis of the phosphoramidite derivatives of 2′-spiro arabinonucleosides **379** and **381** (*Scheme 118*). Ce^{III}-assisted Grignard addition of the allyl group to 3′,5′-di-*O*-(tetraisopropylidinedisiloxane-1,3-diyl)-2′-ketouridine **129b** occurred stereoselectively from the α-face of the furanose to give the key intermediate **377**. Hydroboration of **377** with 9-BBN followed by reaction with mesyl chloride (MsCl) gave the mesylated 2′-hydroxypropylarabinonucleoside derivative **378**. Oxidative cleavage followed by reduction and selective mesylation converted the allyl group of nucleoside **377** to a mesylated 2-hydroxyethyl arabinonucleoside **380** in moderate yield. After



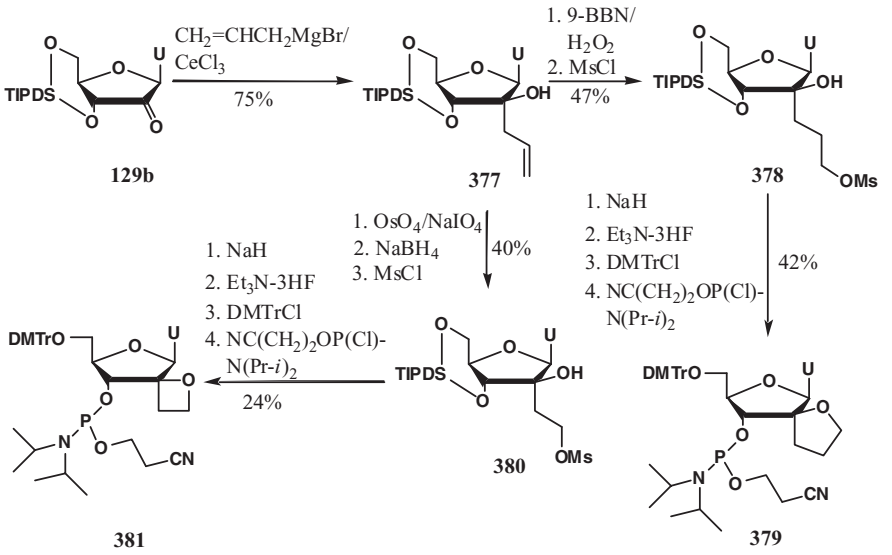
Scheme 116



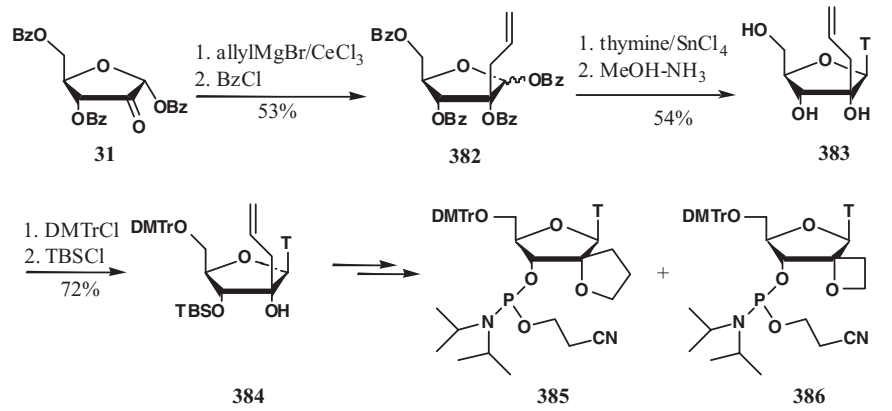
Scheme 117

base-induced cyclization, both **378** and **380** were converted to the corresponding nucleoside phosphoramidites in good yields.

The reaction of allylMgBr-$CeCl_3$with the 2-ketofuranose **31** gave tri-*O*-benzoyl-2-*C*-allyl ribofuranose **382** as an anomeric mixture.Furanose **382** was stereoselectively coupled with persilylated thymine using $SnCl_4$ as a Lewis acid catalyst. Subsequent deprotection of this mixture with saturated methanolic ammonia provided the β-configured 2′-*C*-allyl ribonucleoside **383** in 54% yield. Selective 5′-*O*-dimethoxytritylation followed by 3′-*O*-silylation afforded the key intermediate **384** in 72% yield. The same procedures as described above for the synthesis of **379** and **381** were used to prepare the phosphoramidites **385** and **386** containing an O2′-C2′-linked five- and four-membered rings, respectively (*Scheme 119*).[135]

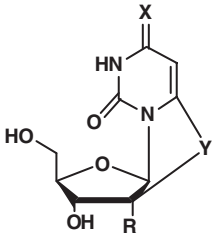


Scheme 118

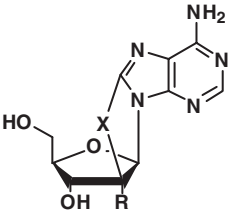


Scheme 119

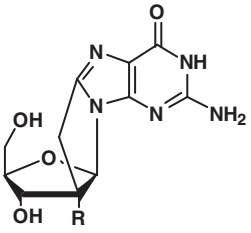
3. 2′-C-Bridge Cyclic Nucleosides



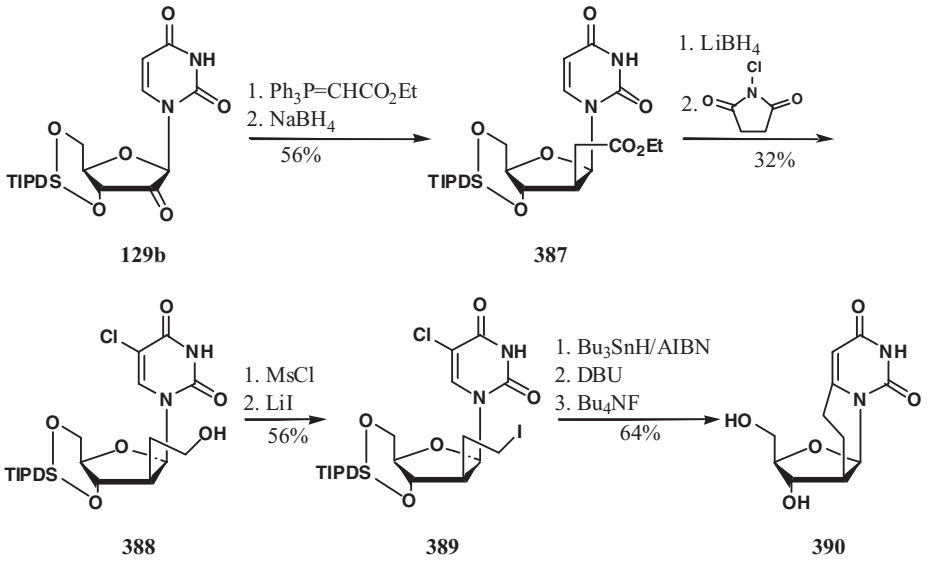
R = H, OH, CH_2OH
X = O, S, NH
Y = CH_2, CH_2CH_2, O, CH_2O



R = H, OH
X = CH_2, CH_2CH_2



R = H, OH



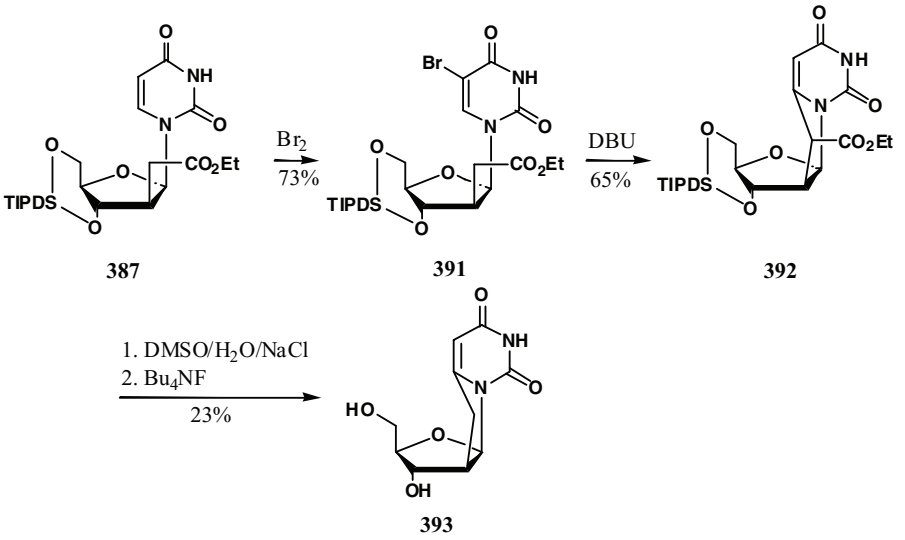
Scheme 120

Ueda *et al.*[136] reported the synthesis of a carbon-bridged cyclouridine, 2′-deoxy-6,2′-ethano-cyclouridine, starting from **129b** *via* the 2′-deoxy-2′-iodoethyl-5-chlorouridine derivative through a radical cyclization (*Scheme 120*). Treatment of **129b** with $Ph_3P = CHCO_2Et$ afforded the Wittig product; subsequent reduction with $NaBH_4$ gave **387** in 56% yield. Treatment of **387** with $LiBH_4$ followed by chlorination using *N*-chlorosuccinimide gave the 5-chloro derivative **388**. Treatment of **389** with Bu_3SnH in the presence of azo*bis*isobutyronitrile (AIBN) followed by dehydrochlorintion with DBU and finally deprotection with TBAF gave the 2′-deoxy-6,2′-ethanocyclouridine **390** in 64% yield (three steps).

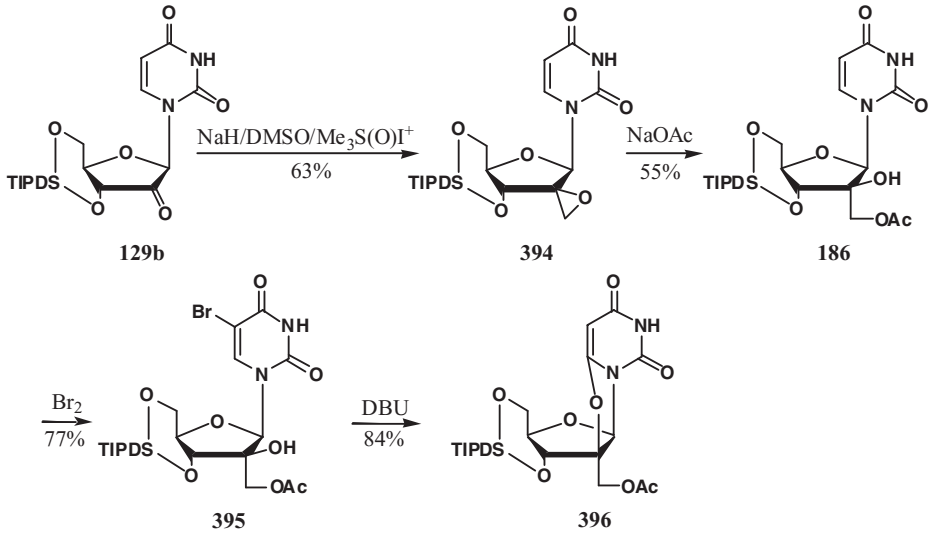
Sano *et al.*[137] synthesized 2′-deoxy-6,2′-methanocyclouridine (**393**) from 3′,5′-*O*-protected 2′-ketouridine **387** (*Scheme 121*). Compound **387** was treated with bromine to give the 5-bromo derivative **391** in 73% yield. Treatment of **391** with *t*-BuOK or NaH did not give the expected product **392**; however, treatment with DBU in refluxing dioxane afforded **392** in 65% yield. Deethoxycarbonylation of **392** with DMSO in water and sodium chloride at 140°C, followed by deprotection with TBAF, gave the 2′-deoxy-6,2′-methanocyclouridine **393** in 23% yield. The circular dichroism (CD) spectrum of **393** showed a strong negative ellipticity, similar to that of 2′-deoxy-6,2′-ethano-cyclouridine (**390**).

Sano *et al.*[137] also reported the synthesis of the O^6,2′-anhydro derivative of arabinofuranosyluracil (*Scheme 122*). Reaction of **129b** with dimethyloxosulfonium methylide at 0°C afforded the 2′-spiro epoxide **394** in 63% yield. **394** reacted with sodium acetate in acetic acid to give **186**. Bromination of **186** with bromine in acetic acid gave the 5-bromo derivative **395**. Dehydrobromination of **395** using DBU gave the O^6,2′-anhydro derivative of arabinofuranosyluracil (**396**).

Sano *et al.*[83] also reported the synthesis of 6,2′-methanocyclouridine, a uridine derivative with a fixed high-anti conformation (*Scheme 123*). Compound **97** was treated with *t*-BuOOH and 0.5% OsO_4 to give a mixture of diols **397** and **398** (**397/398** ∼2:1).



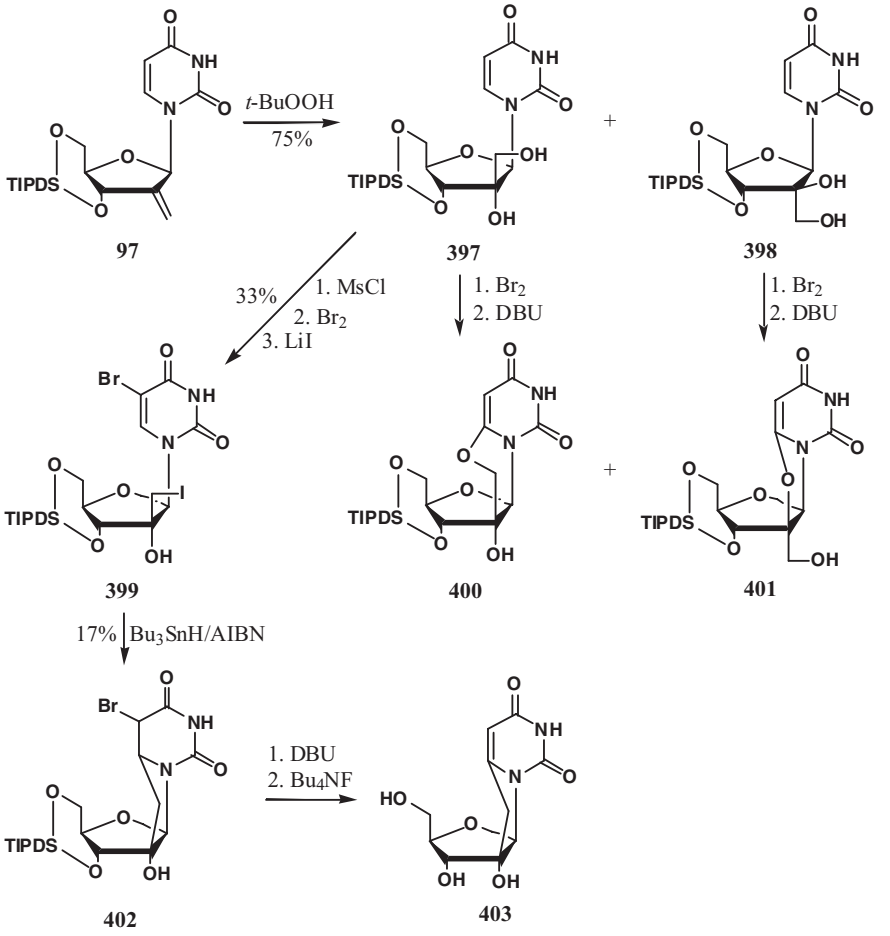
Scheme 121



Scheme 122

Compound **397** was mesylated, brominated at the *C*-5 position and treated with LiI to give 2′-iodomethyl-5-bromouridine (**399**) in 33% yield. Treatment of **399** with Bu_3SnH/AIBN followed by dehydrobromination with DBU and desilylation with TBAF gave 6,2′-methano-cyclouridine (**403**). Bromination of diols **397** and **398** with Br_2 in the presence of AcOH/NaOAc followed by dehydrobromination using DBU gave **400** and **401**, respectively.

Ueda *et al.*[138] reported the conversion of 2′-*C*-nitromethylarabinosyl-5-bromouracil to a carbon-bridged cyclonucleoside through a 2′-nitromethylene derivative (*Scheme 124*). Treatment of 2′-ketouridine **129b** with NaH and CH_3NO_2 gave **404** in good yield.

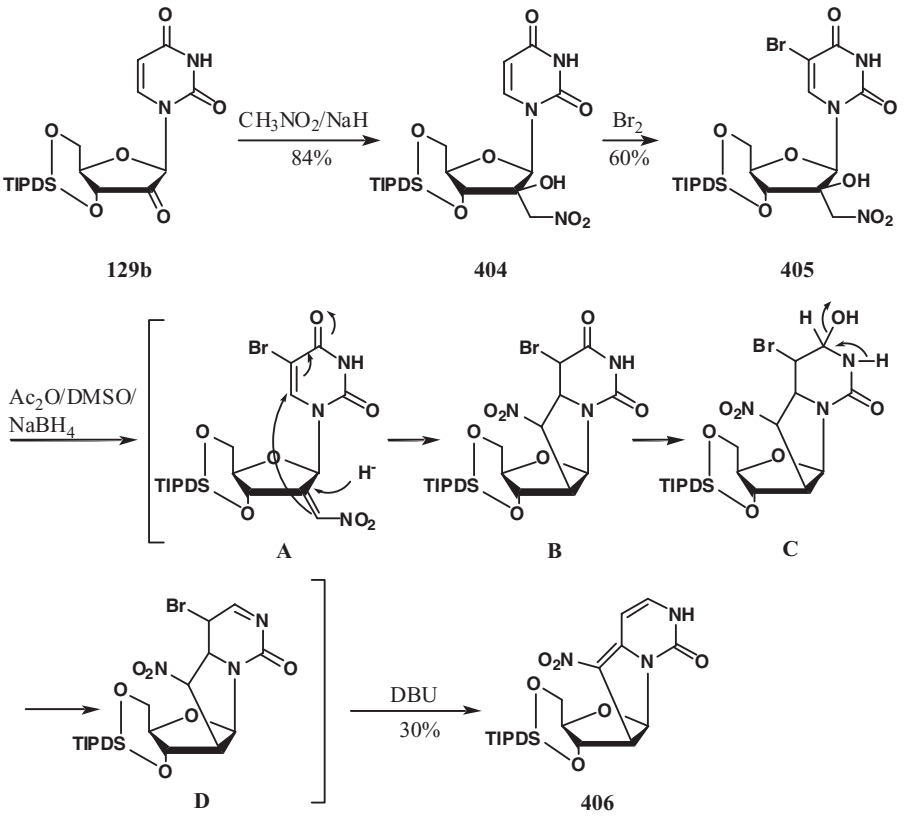


Scheme 123

Compound **404** reacted with Br_2 in acetic acid to give the 5-bromouridine derivative (**405**). Subsequent reaction of **405** with Ac_2O/DMSO, $NaBH_4$ and dehydrobromination using DBU gave the 2′-nitromethyline derivative **406**.

2′-Deoxy-6,2′-methanouridine, 2′-deoxy-6,2′-methanocytidine, and 2′-deoxy-6,2′-methano-4-thiouridine were synthesized by Yoshimura *et al. via* 4-*O*-methyl-6,2′-methanouridine derivative **409** (*Scheme 125*).[139] Condensation of **408** with 2,4-dimethoxy-6-(trimethylsilylmethyl)pyrimidine (**407**) in the presence of BuLi at -60°C afforded a Peterson olefination product, which was then hydrogenated with Pd-C in EtOAc to give the 2-*C*-pyrimidineylmethyl-*arabino*-furanoside (**409**) in good yield. Treatment of **411** with NaOH, or MeOH-NH_3, or H_2S/NaOMe gave 2′-deoxy-6,2′-methano-pyrimidine nucleosides **412** (80% yield), **413** (70% yield) and **414** (70% yield), respectively.

Usui *et al.*[140] synthesized the 2′-deoxy-8,2′-ethanoadenosine from the 2′-ketoadenosine derivative (*Scheme 126*). Reaction of 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-2′-ketoadenosine (**415**) with ethoxycarbonylmethylenetriphenylphosphorane gave the 2′-ethoxycarbonylmethylene derivative, which was reduced to the 2′-hydroxyethyl derivative



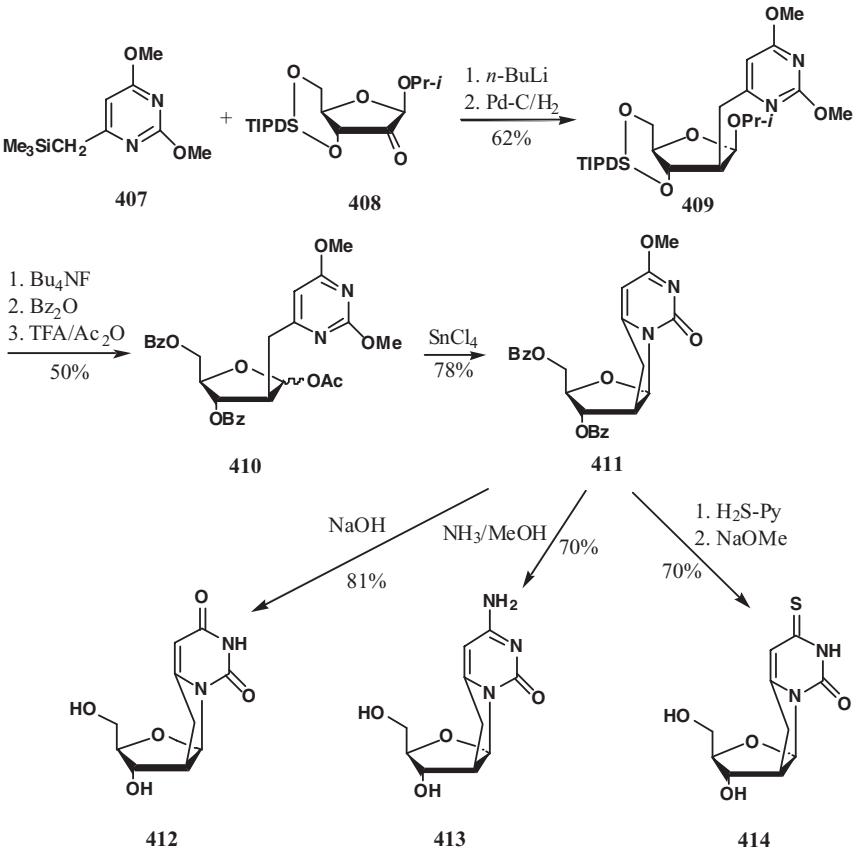
Scheme 124

and then converted to the 2′-iodoethyl-N^6,N^6-dibenzoyladenosine **416**. Compound **416** was cyclized using Bu_3SnH to give **417** in 27% yield. Deprotection of **417** with NH_4OH and TBAF gave 2′-deoxy-8,2′-ethanoadenosine (**418**) in 54% yield.

Matsuda *et al.*[141] also synthesized the 8,2′-ethano adenosine **422** from 8-bromo-2′-*O*-tosyladenosine (**419**). Reaction of **419** with MeSNa followed by acetylation and oxidation with $KMnO_4$ gave **420** in 81% yield. Substitution of **420** with the sodium salt of diethyl malonate in THF at reflux temperature gave the cyclized nucleoside **421** in 79% yield. Decarboxylation of **421** with 85% aq. pyridine followed by deacetylation using NH_4OH gave the corresponding 8,2′-ethano adenosine **422** (65% yield) (*Scheme 127*).

Magnin *et al.*[142] reported that a vinyl functionality at the 8-position of adenosine derivative **423** reacts intramolecularly with a *C*-2′ radical, generated using Bu_3SnH and a catalytic amount of AIBN, to give a 6-endocycloproduct (**424**) in 65% yield (*Scheme 128*).

Usui *et al.*[143] reported the synthesis of 8,2′-methano- and 8,2′-ethanoadenosine from 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-2′-ketoadenosine (*Scheme 129*). Reaction of **415** with methylenetriphenylphosphorane gave the corresponding 2′-methylene derivative. After hydroxylation with OsO_4, the 2′-methylene derivative was converted to the 2′-phenylthiomethyl derivative (**425**) in 16% yield. Irradiation of **425** using a low-pressure

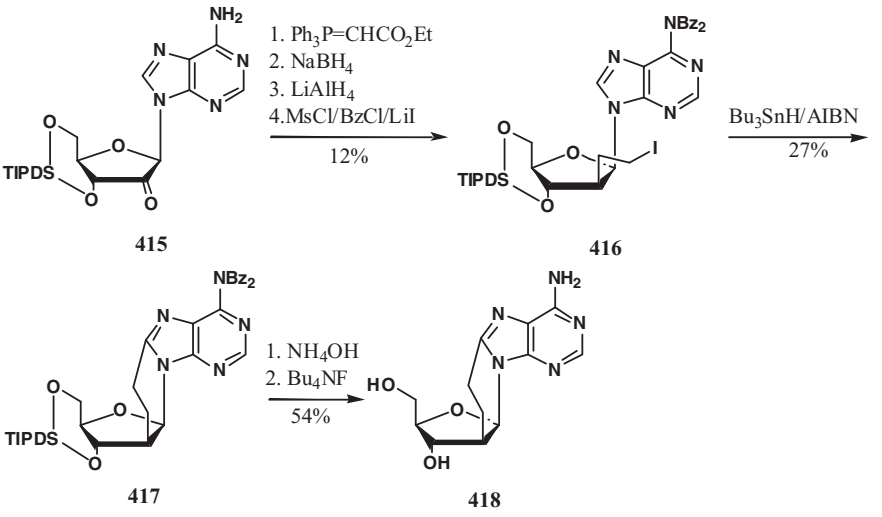


Scheme 125

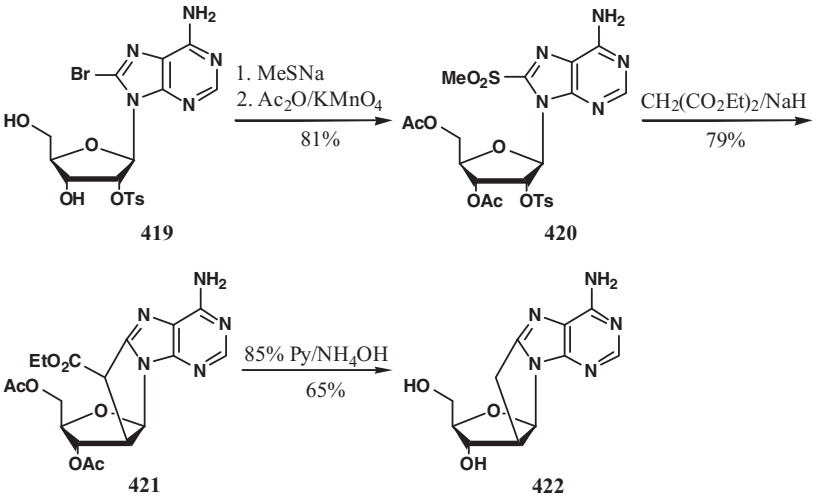
Hg lamp in the presence of $(MeO)_3P$ followed by desilylation with TBAF gave the 8,2′-methanoadenosine **426** in 22% yield. Using a similar procedure, 8,2′-ethanoadenosine **429** was also prepared from 2′-ketoadenosine derivative **415** in 3% overall yield (eight steps).

Similarly, Usui *et al.* obtained 8,2′-methanoguanosine (**433**) starting from N^2,2′,3′,5′-*O*-tetraacetylguanosine (**430**)[144] (*Scheme 130*). Compound **430** could be converted to the 2′-methylidene derivative (**431**), which was an approximately equimolar mixture of anomers, in 7% overall yield (four steps). Oxidation of **431** with OsO_4 followed by mesylation and substitution with thiophenoxide gave 2′-phenylthiomethylguanosine **432** in 23% yield. Photocyclization of **432** followed by removal of the sugar and base protecting groups furnished 8,2′-methanoguanosine (**433**) in 13% overall yield (four steps).

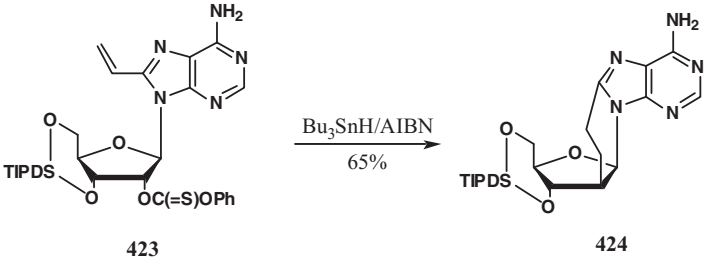
2′-Deoxy-8,2′-methanoguanosine (**438**) was also synthesized by Matsuda *et al.*[145] (*Scheme 131*). Reaction of tri-*O*-acetyl-8-bromoguanosine (**434**) with $Ph_3P/EtO_2CN = NCO_2Et$ and MeSNa gave **435** in 82% yield. Compound **435** could be converted into the 8-methylsulfone **436** (70% yield) in five steps (acetylation, selective deacetylation, tosylation, reacetylation and oxidation). Treatment of **436** with $NaH/CH_2(CO_2Me)_2$ followed by decarboxylation with 85% aqueous pyridine gave the decarboxylated methano derivative



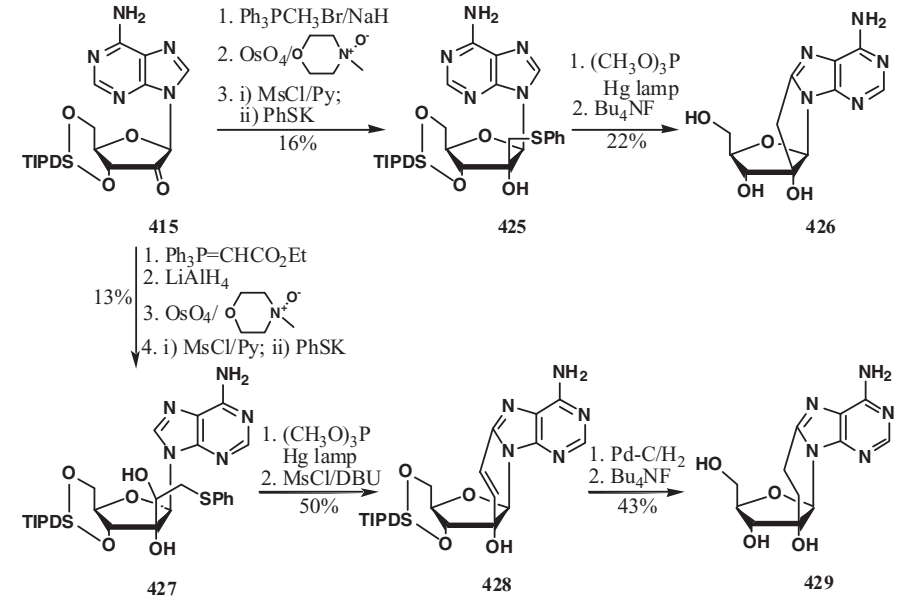
Scheme 126



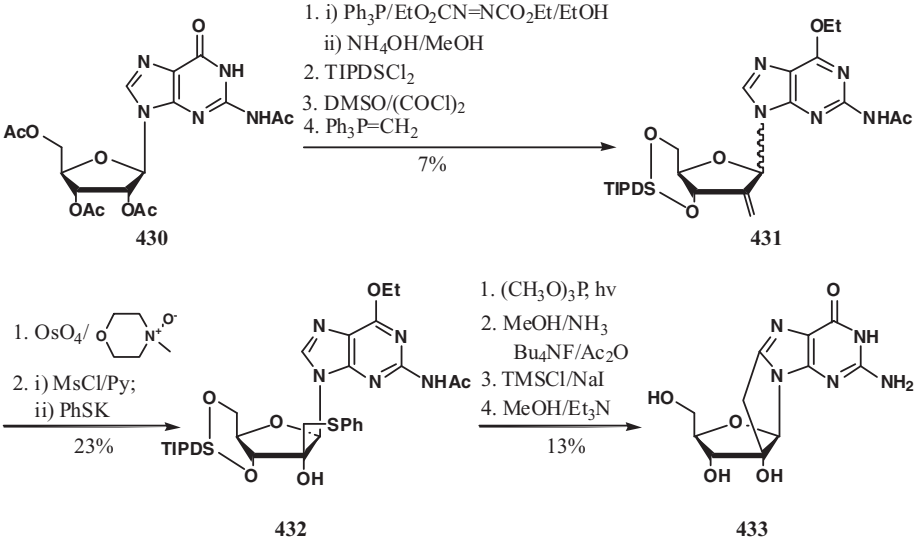
Scheme 127



Scheme 128



Scheme 129

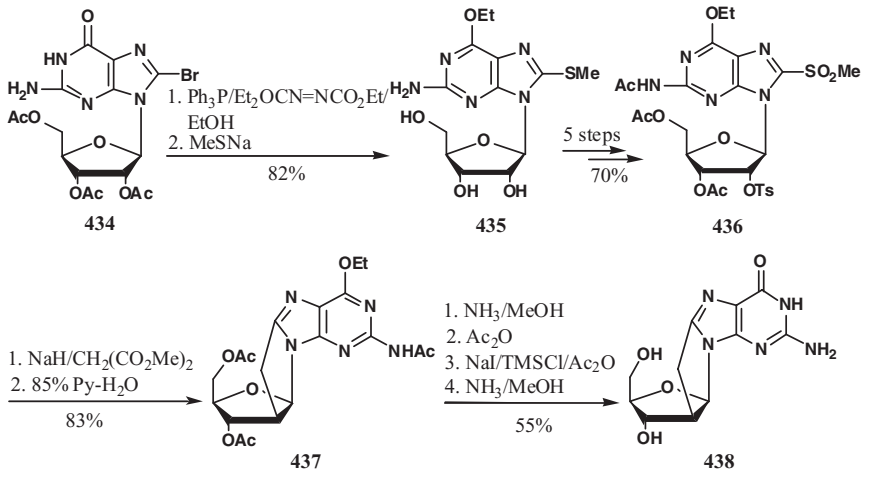


Scheme 130

(**437**) in 83% yield. Deprotection of **437** in four steps gave 2′-deoxy-8,2′-methanoguanosine (**438**) in 55% overall yield.

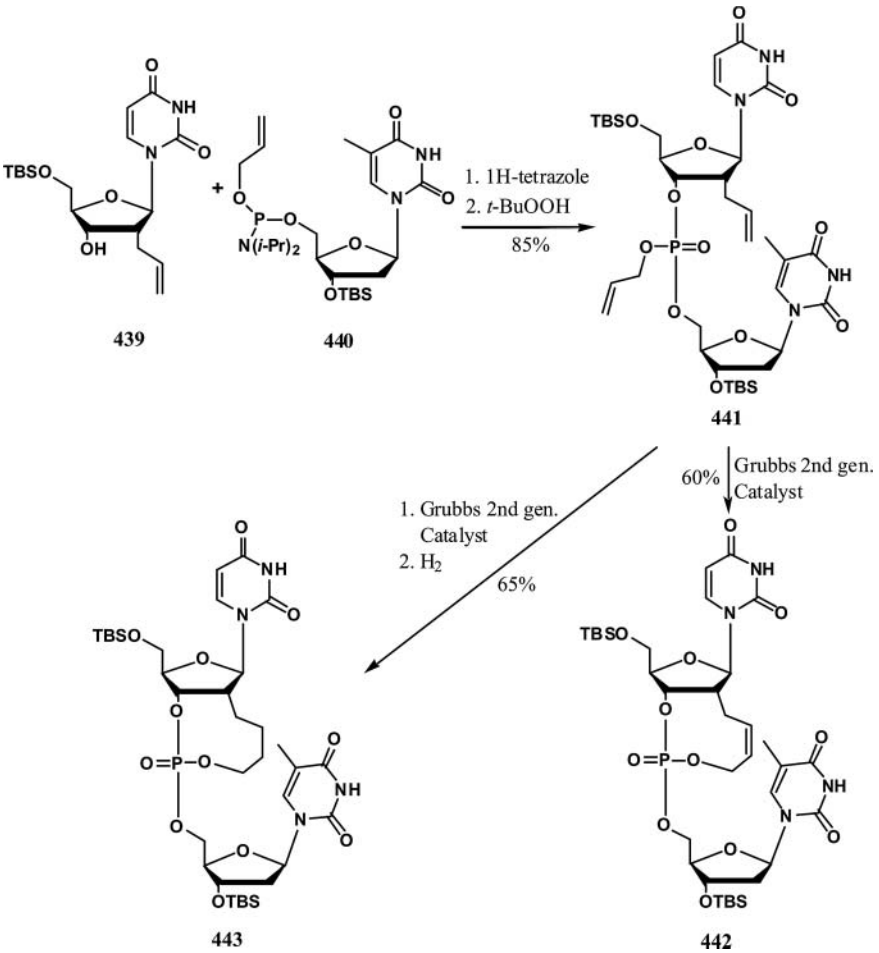
4. 2′-C-Cyclic Dinucleosides

Nielsen *et al.*[146,147] described the synthesis of a new type of cyclic dinucleotide with a butylene linker (**442** and **443**; *Scheme 132*) or a propylene linker (**446** and **447**; *Scheme*



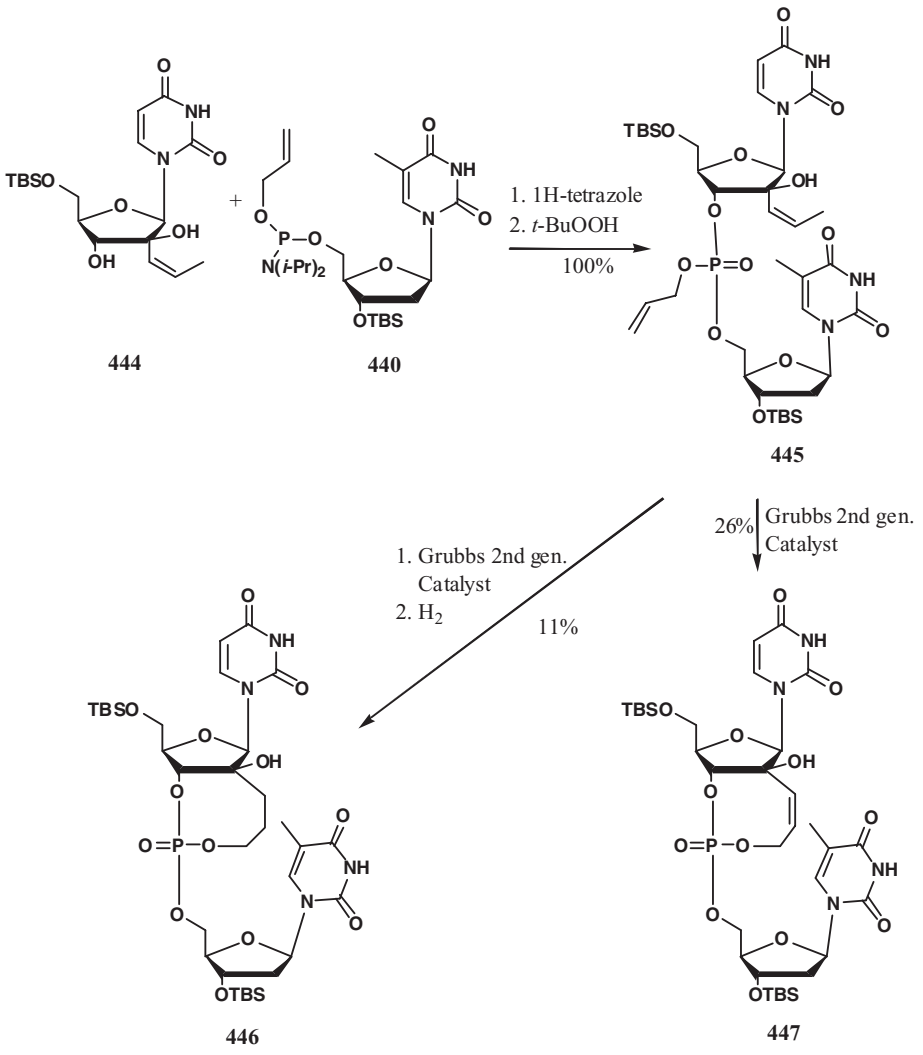
434 **435** **436** **437** **438**

Scheme 131



439 **440** **441** **442** **443**

Scheme 132



Scheme 133

133) between the upper 2′-*C* position and the 3′-*O*-phosphate linkage *via* a tandem ring-closing metathesis. The nucleoside building blocks **439** and **440** were coupled by treatment with 1*H*-tetrazole followed by oxidation to give the diallylic dinucleotide **441** in a high yield as a mixture of two phosphorus epimers in an approximately 2:1 ratio. This epimeric mixture was subjected to a standard RCM protocol using Grubbs 2nd generation catalyst to give **442** in 60% yield. Meanwhile, the application of the tandem RCM hydrogenation protocol with **441** as the substrate afforded the saturated cyclic dinucleotide **443** in 65% isolated yield. Using the same conditions, cyclic dinucleotides **446** and **447** were prepared in low yields.

In summary, a fairly extensive range of 2′-*C*-branched nucleosides has been synthesized and examined for potential antiviral, anticancer and antisense activity. Some of the

2′-*C*-branched nucleosides such as **3b**, **5a**, **81b**, and **222a** exhibited strong antiviral activity. Combinations of 2′-*C*-modifications with other modifications elaborated within the vast literature on nucleoside analogues offer many potentially promising avenues for future study. Although this review has focused on analogues that branch at C-2 of ribose, both C-3, and C-5 also represent potential sites for branching the carbohydrate moiety. In the past several years, small RNAs including microRNAs, small interfering (si) RNAs, and piwi-interacting (pi)RNAs have emerged as important cellular regulators of gene expression that operate through a variety of mechanisms.[148] A current paradigm in drug development entails exploitation of these natural pathways to control expression (and therefore activity) of targeted genes with siRNA. Chemical modifications have been shown to improve the efficacy of siRNAs, but so far only a limited range of modifications have received attention.[149,150] Additionally, the potential of branched nucleic acids to impart favorable properties to RNA drugs remains largely unknown. Exploring this potential will require synthesis of phosphoramidite derivatives for incorporation into oligonucleotides, which would render 2′-*C*-branched nucleosides more broadly accessible to the pharmaceutical and RNA communities.

Nucleobases Abbreviations

B	=	base
A	=	adenine
A^{Bz}	=	N^6-benzoyladenine
C	=	cytosine
C^{Ac}	=	N^4-acetylcytosine
C^{Bz}	=	N^4-benzoylcytosine
C^{MMTr}	=	N^4-(Monomethoxytrityl)cytosine
G	=	guanine
G^{Ac}	=	N^2-acetylguanine
G^{CHNMe_2}	=	N^2-(dimethylaminomethylene)guanine
U	=	uracil
T	=	thymine

Acknowledgements

The authors gratefully acknowledge the support of this work by Howard Hughes Medical Institute and NIH (grant 1R56AI081987–0109 to J.A.P.). They also thank the following members of the Piccirilli group for proofreading the manuscript: E. Leung, N. Suslov, N. Tuttle, K. Sundaram, and J. Frederiksen.

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