American Journal of Chemistry 2013, 3(4): 77-95
DOI: 10.5923/j.chemistry.20130304.01

A Global Perspective on a Review of a Three-Year C-Nucleosides Development: 2009-2011

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Abstract C-Nucleosides remain among the most challenging modified nucleosides to build for evaluation of their biological activities. This review includes a brief introduction of the C-Nucleosides classification and focuses on what has been done during a three year period (2009-2011) for their synthetic approaches and structural modifications. It spots locations of work and synthetic tactics, then correlate that to international *vs.* national transformation of methodologies. For sustainable developments science diplomacy may provide a forum for international collaborative research, which leads to intriguing topics of potential applications.

Keywords C-nucleosides, Synthetic Strategies, Global Perspective, Science Diplomacy

1. Introduction

Nucleosides are fundamental building blocks of biological systems. The natural nucleosides and their analogs find numerous applications as antibiotic, fungicidal, anti-tumor and anti-viral agents. Therefore, the chemistry of these compounds has been studied extensively and today nucleoside chemistry represents an important area of research for modern drug discovery. Vital elements of the structure of nucleoside are: 1) hydroxymethyl functionality; 2) spacer [e.g., sugar component] on which the hydroxymethyl group is a part; 3) heteroaryl base or aryl group attached to the sugar. C-Nucleosides are a subtype of these compounds in which the spacer and heteroaryl(aryl) groups are linked *via* C-C bond (Figure 1). The attractive feature of C-Nucleosides arises from the presence of this C-C glycosidic bond, which gives a greater resistance towards chemical and enzymatic hydrolysis than N-Nucleosides.

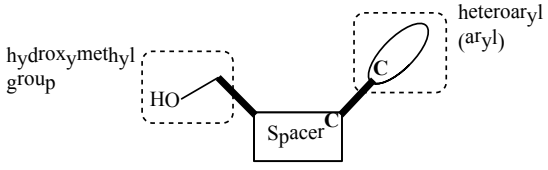

Figure 1. Generalized structure of a C-nucleoside analogue

C-Nucleosides can be classified according to their sugar moiety into five different categories:

1- Cyclic C-Nucleoside
2- Acyclic C-Nucleoside
3- Homocyclic C-Nucleoside
4- Reverse C-Nucleoside
5- Carbocyclic C-Nucleoside
6- Heterocyclic C-nucleoside

These features have motivated organic chemists to develop efficient and practical synthetic methods, and numbers of strategies have been devised to design nucleoside analogues: 1) building up the heterocyclic unit on a suitably functionalized carbohydrate moiety; 2) building up a carbohydrate moiety on a suitably functionalized heterocyclic compound; 3) transformation of C-Nucleoside into another; 4) direct coupling between a suitably protected carbohydrate moiety with a preformed heterocyclic compound.

In this report we wish to view the latest development (2009-2011) with spot lighting on the tactics chemists deliberate based on their location(s).

2. Building up the Heterocyclic Unit on a Suitably Functionalized Carbohydrate Moiety

2.1. From Nitrile Terminal on C1 Atom

2.1.1. Cyclic C-Nucleosides

Functionalization of the carbohydrate moiety with nitrile group at the anomeric carbon gave an important precursor for synthesis of C-Nucleoside. Protected ribofuranosyl nitrile **5a-c** was converted to the corresponding ribofuranosyl

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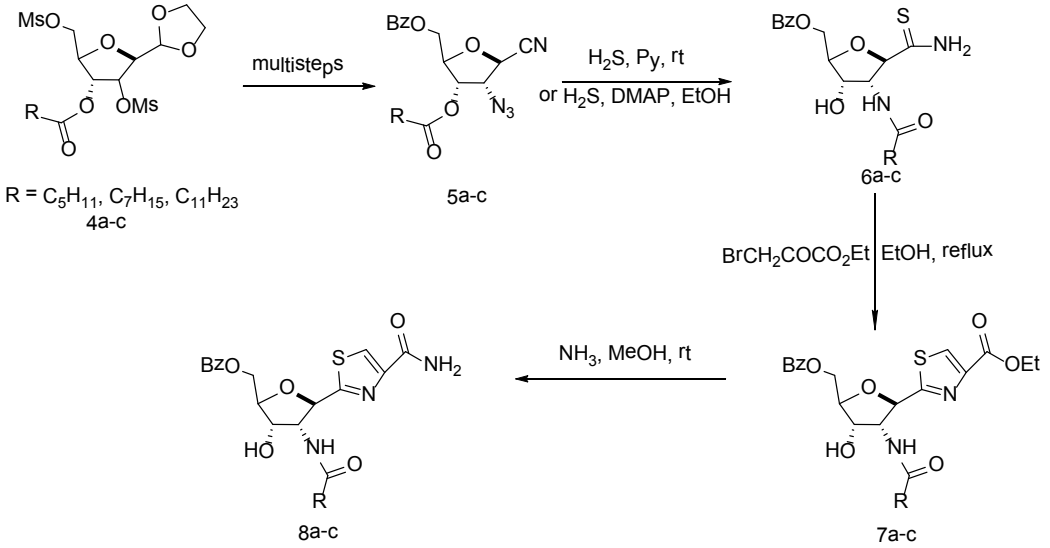
Published online at http://journal.sapub.org/chemistry

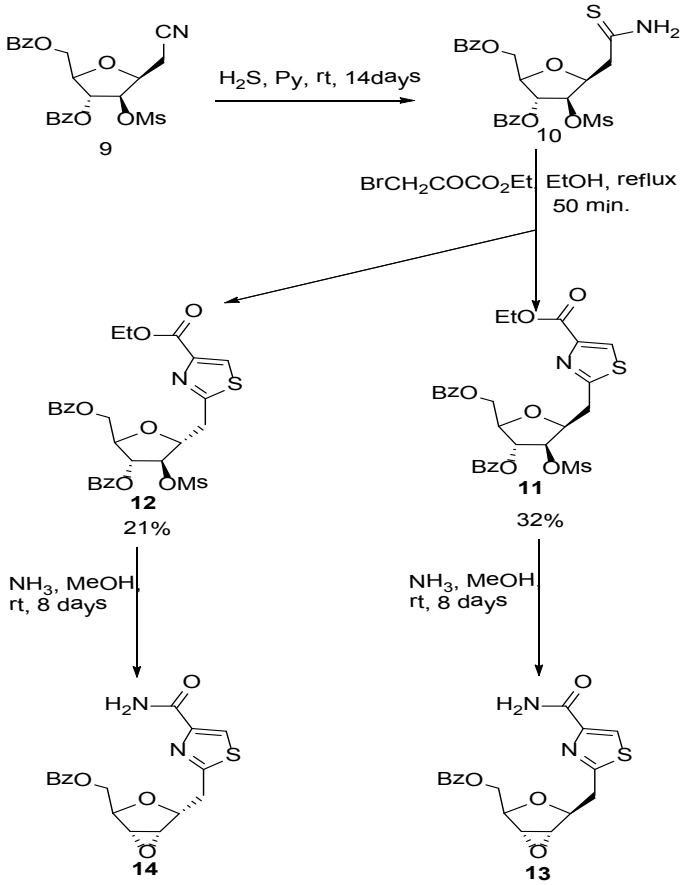
thioamide **(6a-c)**, whose reaction with ethyl bromopyruvate gave the protected tiazofurin derivative **7a-c**. Treatment of the latter with methanolic ammonia afforded The thiazole C-Nucleoside **8a-c** (Scheme 1). [1,].



Scheme 1. Construction of C-nucleosides **7** from nitrile precursors

2.1.2. Homocyclic C-Nucleosides

The homocyclic C-nucleoside analogue was also reported from the nitrile **9** using the same procedure already used for preparation of **8a-c** to give the corresponding homo-C-tiazofurin analogue bearing 2,3-anhydro ribofuranosyl moiety **13** and **14,** which represent the first biologically active tiazofurin analogue that demonstrate antiproliferative activity (Scheme 2). [2,].

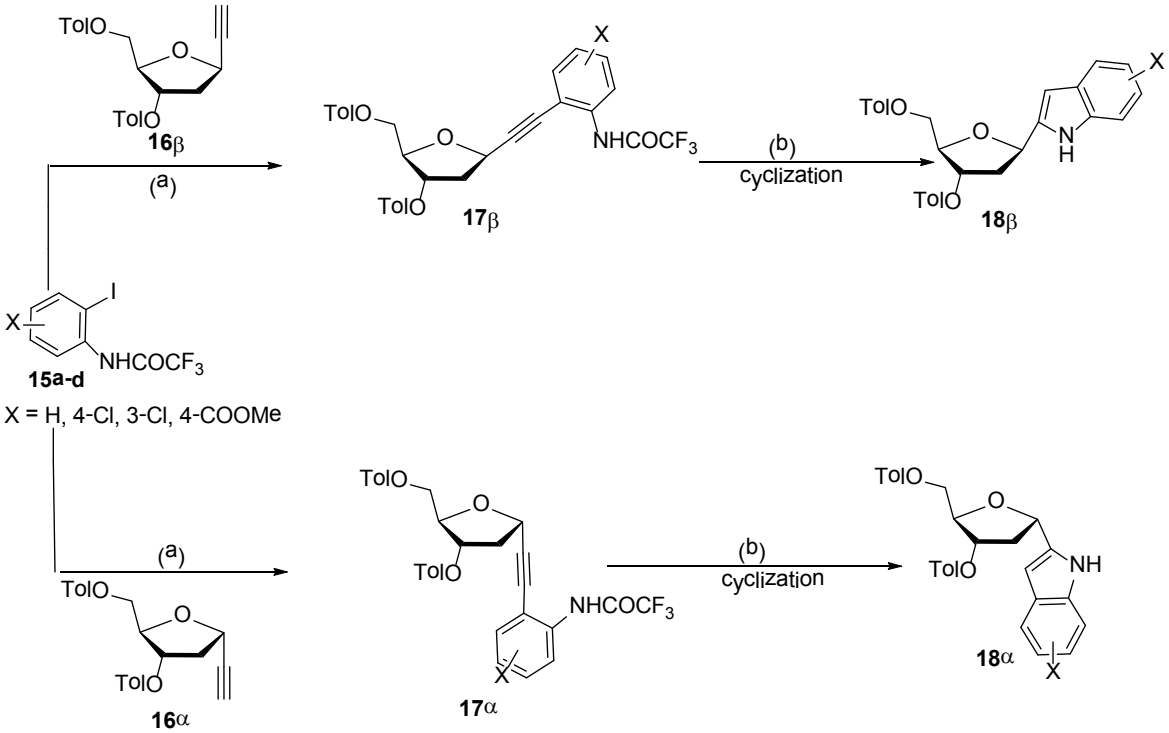


Scheme 2. Construction of homocyclic C-nucleoside **13** from nitrile precursor

2.2. From Alkynyl Terminal on C1 Atom

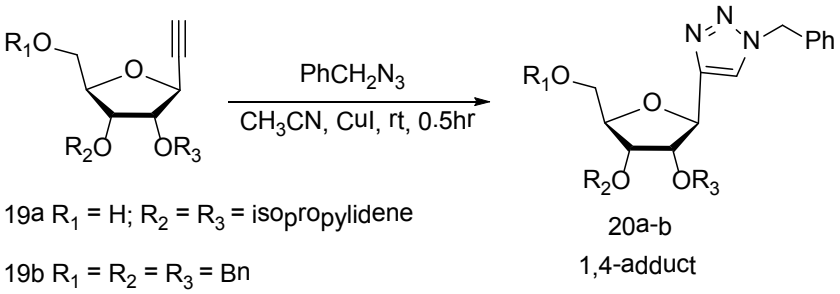
2.2.1. Cyclic C-Nucleosides

Another essential functional group for synthesis of hetrocyclic moiety upon carbohydrate is the ethynyl group at the anomeric carbon. Sonogashira reaction of 1-ethynyldeoxyriboside **16α** or **16β** with trifluoroacetanilide derivatives **15a-d** furnished the corresponding alkynyldeoxyribose derivatives **17α** or **17β**, whose cyclization led to indolyl C-Nucleoside **18α** or **18β** (Scheme 3). [3,].



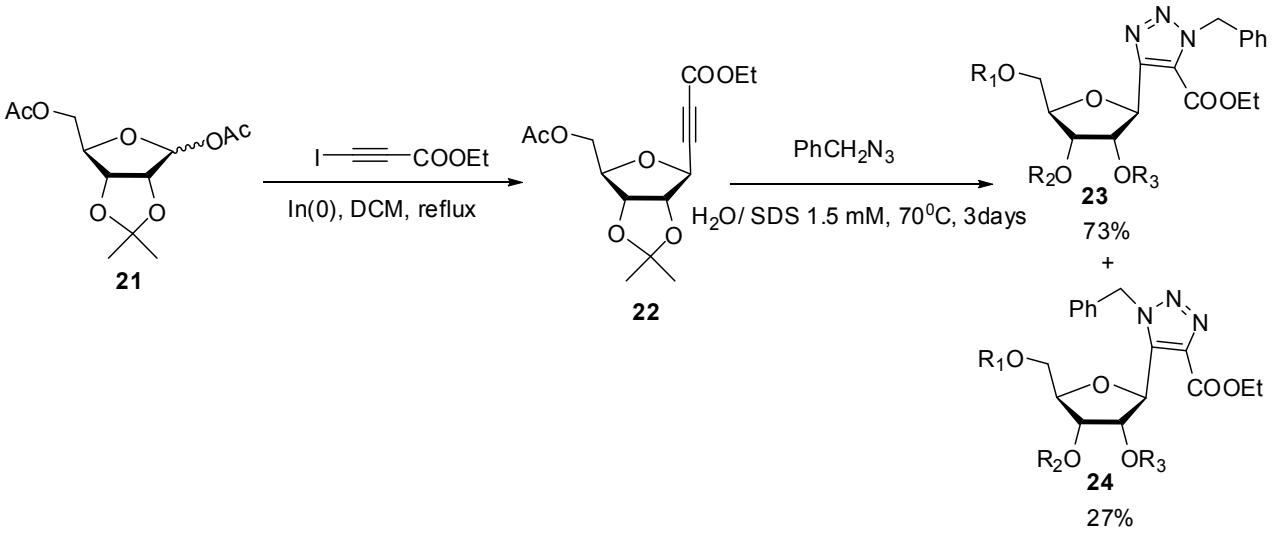
Scheme 3. Synthetic steps to prepare C-nucleoside **18** from alkynyl precursor

Monosubstituted ribosyl acetylene **19a-b** was also used for a 1,3- dipolar cycloaddition with benzylazide in presence of copper catalysis to direct the formation of only 1,4 disubstituted regioisomer of 1,2,3-triazole C-Nucleoside **20a-b** which is considered as carbonylated analogue of ribavirin (Scheme 4). [4,].



Scheme 4. Synthesis of 1,2,3-triazole C-nucleosides **20** from alkynyl precursor

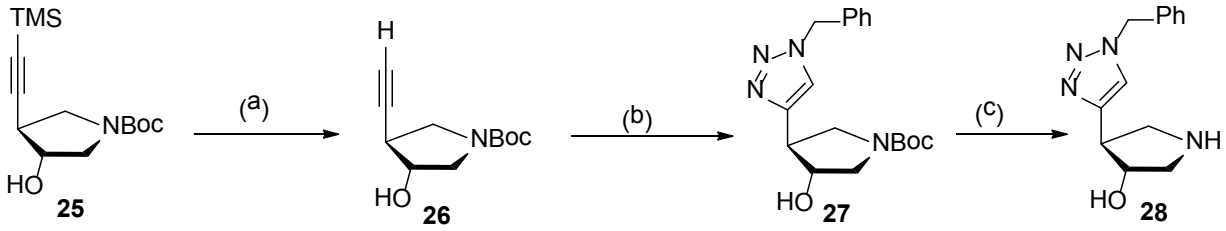
Disubstituted ribosyl alkyne **22** obtained from riboside **21** using indium(0)-mediated alkynylation reaction was also involved into 1,3-dipolar cycloaddition reaction with benzylazide to afford 1,4,5-trisubstituted triazole C-Nucleosides **23** and **24** (Scheme 5). [4,] The reaction was conducted under micellar catalysis to improve the regioselctivity.



Scheme 5. Synthetic approach to C-nucleosides 23 and 24 via 1,3-dipolar cyclization

2.2.2. Heterocyclic C-Nucleosides

The same methodolgy of heterocyclization of ethynyl group into 1,2,3-triazole was used to prepare the aza-C-Nucleoside analogue **28** (Scheme 6). [5, ,].



(a) TBAF (1 M in THF), THF, rt
(b) $PhCH_2N_3$, sod. ascorbate, $CuSO_4$, t-BuOH, H_2O, rt
(c) 36% aq HCl, MeOH, rt

Scheme 6. Synthetic approach to aza-C-nucleosides 28 *via* 1,3-dipolar cyclization

2.3. From Carbonyl Functionality on C1 Atom

2.3.1. Cyclic and Homocyclic C-Nucleosides

Hantzsch reaction on the aldehydo of **29a** with β-ketoester **30** and enamine ester **31**, under L-proline catalysis gave dihydropyridine C-Nucleoside **32a** in stereoselective manner with (de 95%). The use of C-glycosyl aldehyde with elongated chain **29b-f** extends the synthesis to the homo-C-Nucleoside analogue **32b-f** (Scheme 7). [6, ,].

Wittig type reaction of sugar functionalized with keto group at the 4-position **33** and stabilized phosphrane leads to **34** whose mild oxidation with pyridinium chlorochromate (PCC) afforded β-sugar- β-formy-α-β-unsaturated ester **35**. Utilization of **35** in cyclocondensation reaction with hydrazine hydrate or its derivatives gave pyrazole, pyrazoline, pyridazionone pseudo C-Nucleoside (Scheme 8). [7,].

2.3.2. Acyclic C-Nucleosides

Construction of the heterocyclic moiety on sugar can also be used for synthesis of acyclo C-Nucleoside analogs. Thus, the condensation of heterocyclic hydrazine derivatives with some monosaccharide gave the corresponding aldehydo sugar hydrazones, which on acetylation gave the *o*-acetylated sugar derivatives subsequent oxidative cyclization followed by de-*o*-acetylation afford the 1,2,4-triazole C-nucleoside. Scheme 9 [8-14, ,].

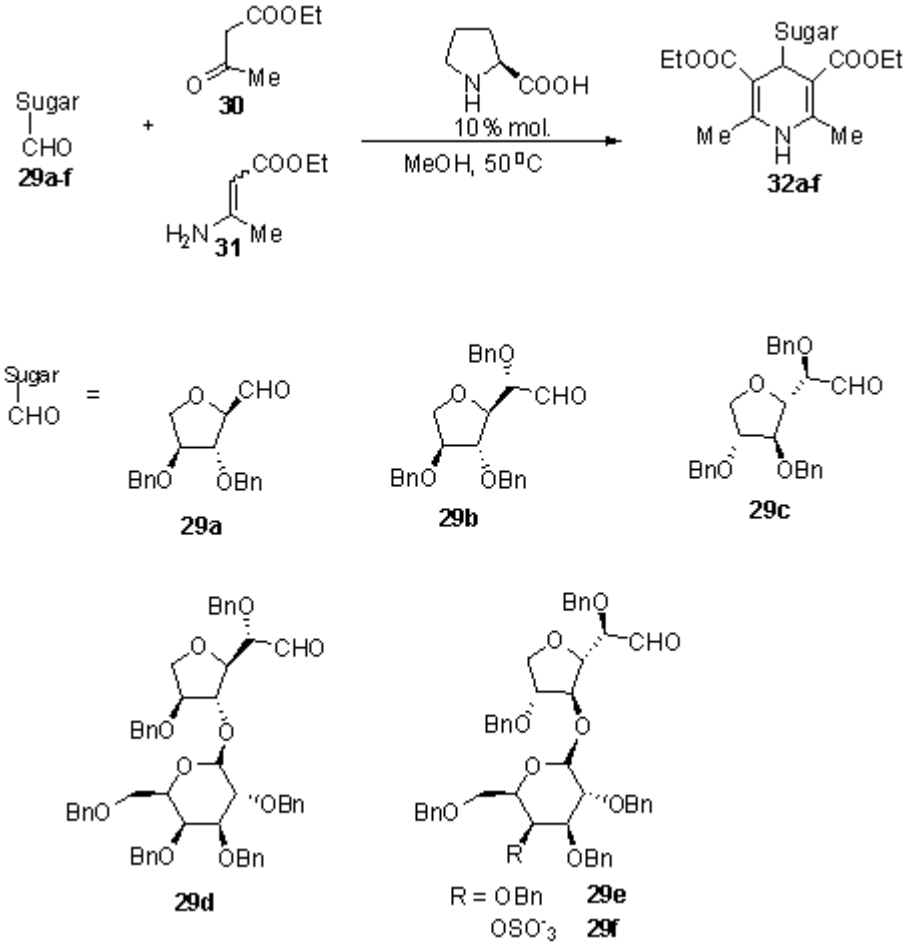
In most cases acetylation of the sugar hydrazones (**40** a, b, c, f, g) gave directly the *O*- acetylated cyclic C-nucleoside, on the other hand all attempts dehydrogeative cyclization of sugar hydrazone (**40d**) or its acetylated derivative (**41 d**) failed. Competition between two *ortho* ring nitrogen (NH, =N) in the oxidative cyclization process such as in case of the *O*-acetylated hydrazone (**41c**, **g**, **h**) gave product corresponded to cyclization between the azomethine carbon and the hydrogenated nitrogen of the ring.

Reaction of acid hydrazides with some aldehydo sugars gave the corresponding sugar aroylhydrazones. When those hydrazones were heated in acetic anhydride at 100°C their corresponding 1,3,4-oxadiazoline acyclic C-nucleosides **46a-b** were isolated (Scheme 10). [15-16, ,].

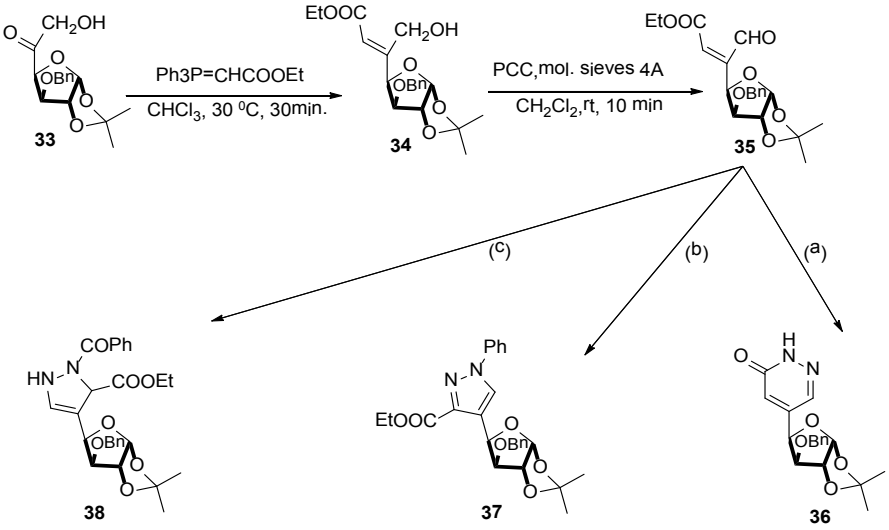
Cyclocondensation of aldehydo sugar Schiffbase **48** with thioglycolic acid in dry dioxane afforded the corresponding thiazolidinone a cyclic C-nucleoside **49** (Scheme 11). [17,].

Following the Hantzch approach for synthesis of pyridine, treatment of D-glyceraldehyde **50** with methyl acetoacetate and dimedone **52** in presence of bentonite clay as a support , ammonium nitrate as source of ammonia, and HNO_3 as oxidant was furnished, after chromatgraphic purification, C-acyclic pyridine nucleoside 53 (Scheme 12).. [18, ,]

The Kidawai's method for synthesis of imidazole derivative *via* condensation of 1,2- dicarbonyl compound such as benzil with aldehyde in excess of ammonium hydroxide under microwave irradiation (MWI) was used for the synthesis of imidazole C-acyclic nucleoside 59 by utilizing the aldehydo functional group of protected D-glyceraldehyde **54**. While condensation of **54** with ethyl acetoacetate and urea using natural phosphate doped with $ZnCl_2$ under MWI afforded acyclic C-nucleoside having dihydropyrimidinone **55**. An efficient synthesis of the C-acyclic nucleoside of indeno[1,2-b]pyridine derivative **62** was accomplished using MWI treatment of **54** with 1,3-indeno-1,3-dione in presence of ammonium acetate (Scheme 13). [18, ,]

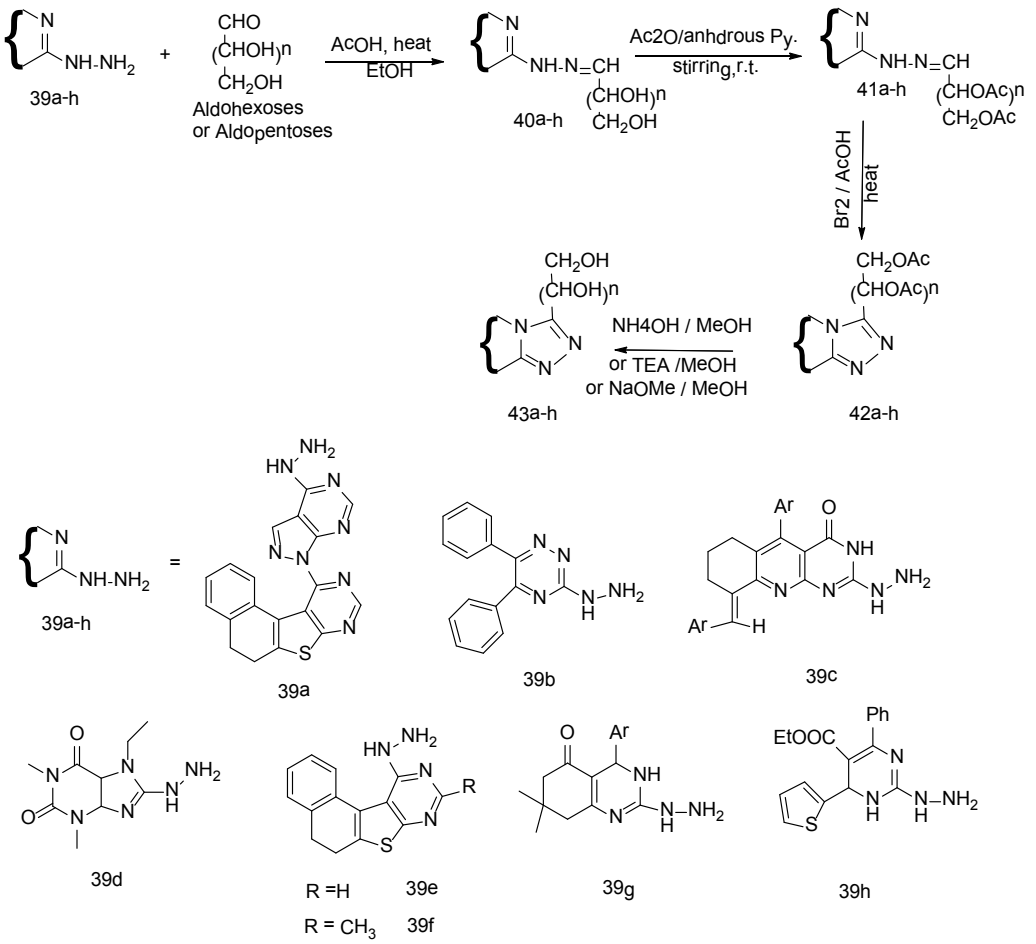


Scheme 7. Construction of cyclic and homocyclic C-nucleosides **32** from carbonyl functionality on C1 of precursors

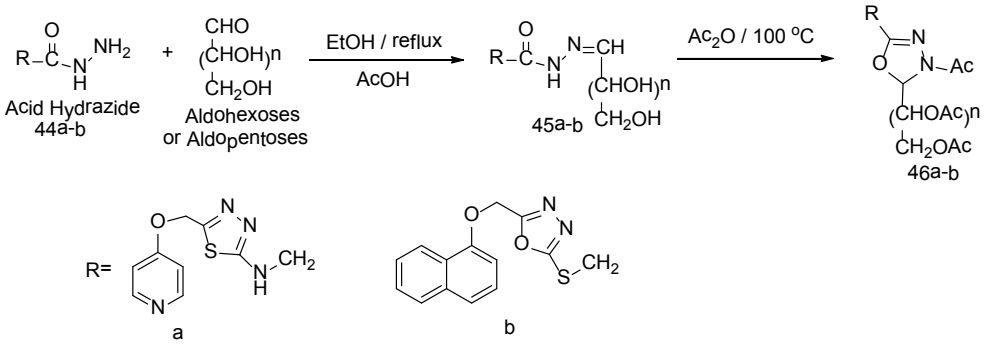


(a) = NH2NH2.H2O, EtOH, reflux
or NH2NH2.H2O, EtOH, MW (450)
(b)= PhNHNH2, EtOH, AcOH, 80 0C
(c) = i- H2NNHCOOMe or H2NNHCOPh
(EtOH, reflux or EtOH, MW (450) or EtOH, AcOH, 80 0C)
ii-Ac2O, NaOAc, 100 0C, 4hr

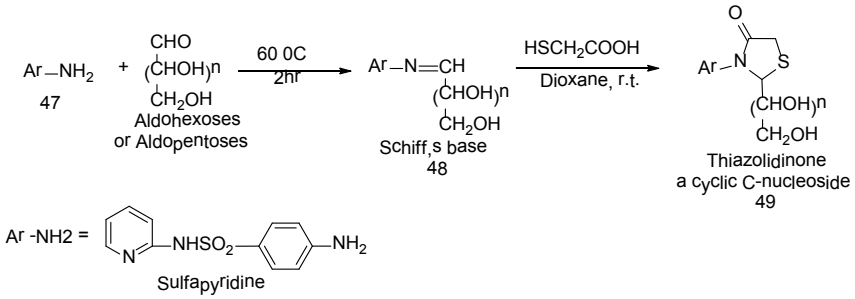
Scheme 8. Syntheses of C-nucleosides **36-38**



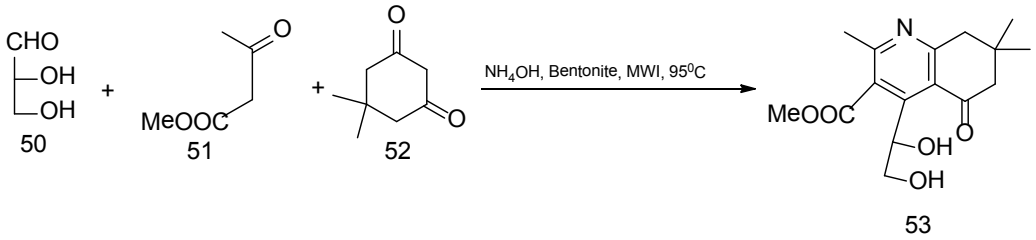
Scheme 9. Synthetic steps for the preparations of acyclic C-nucleosides **43** from the reactions of heterocyclic hydrazines with aldoses



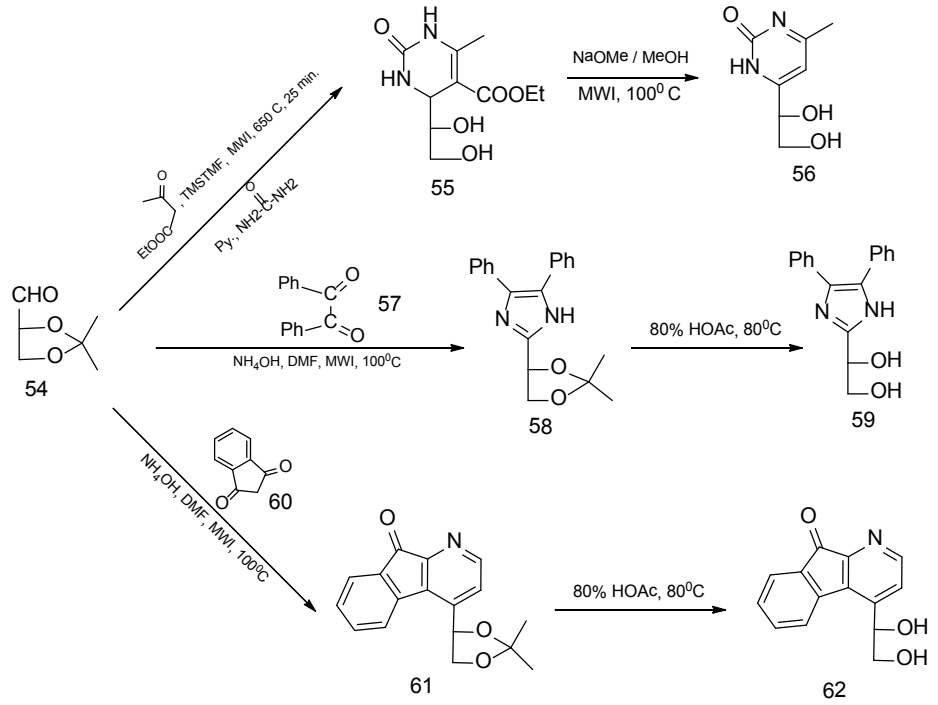
Scheme 10. Synthetic approach to acyclic C-nucleosides 46 from hydrazides



Scheme 11. Synthetic approach to acyclic C-nucleosides **49** from aniline derivatives and aldoses



Scheme 12. Synthesis of acyclic C-nucleoside **53** from aldoses *via* multicomponent reaction (MCR)

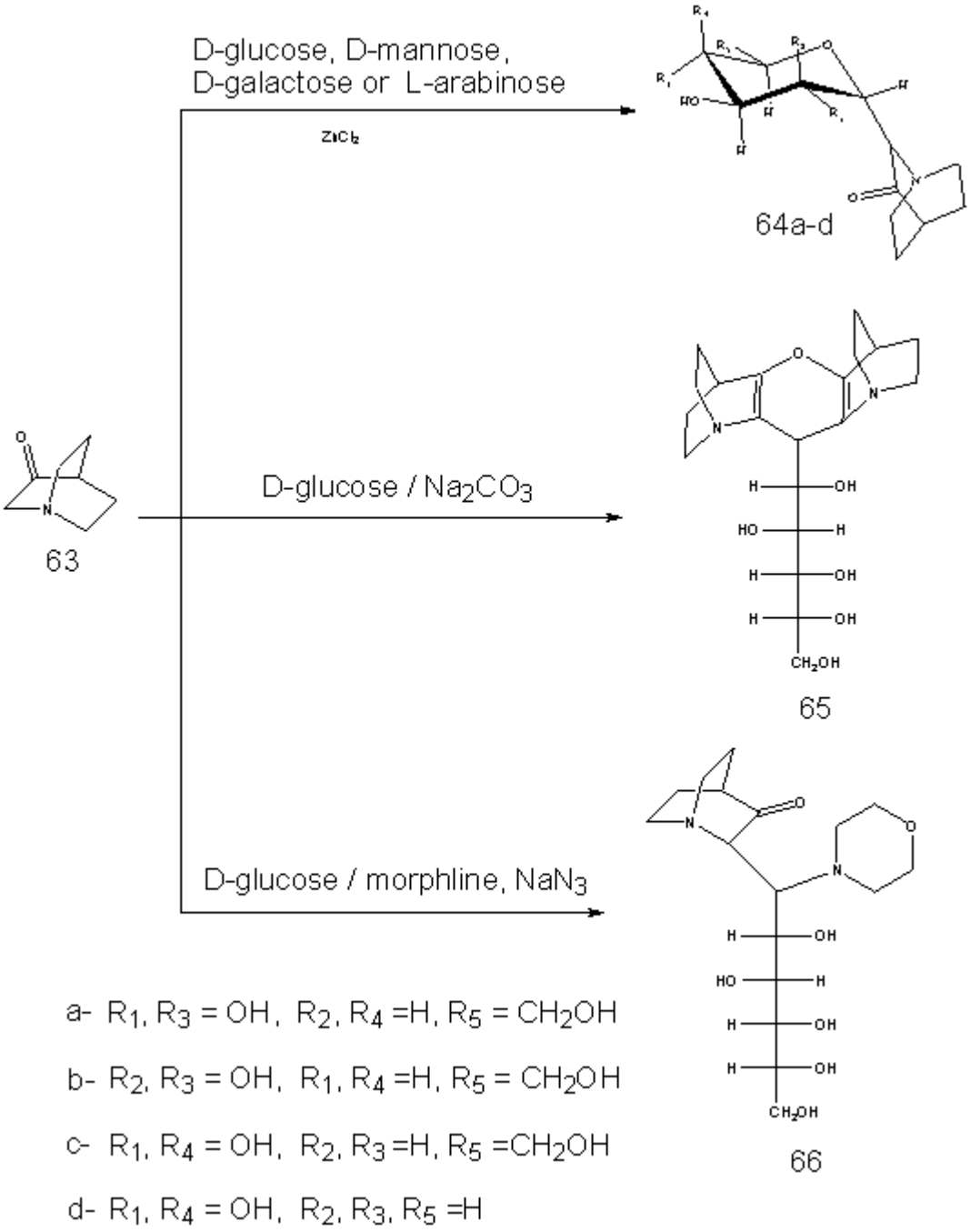


Scheme 13. Synthetic approachs to acyclic C-nucleosides **56, 59** and **62**

3. Direct Coupling between a Suitably Protected Carbohydrate Moiety with a Preformed Heterocyclic Compound

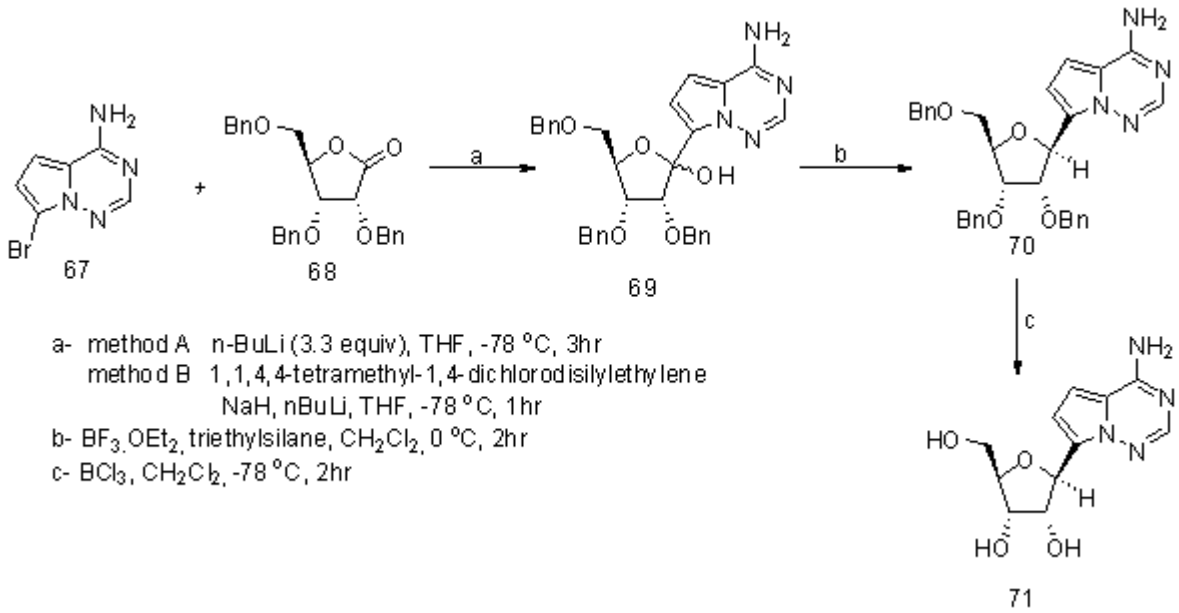
The direct attachment of a preformed glycon unit to an appropriate carbohydrate is one of the most important method for synthesis of C-nucleoside. This strategy is based on ionic, free radical or metal mediated carbon-carbon bond formation.

Synthesis of nucleoside derivatives of quinuclidin-3-one 63 was achieved by the reaction of 63 with D-glucose in presence of catalytic amount of zinc chloride to give the cyclic C-nucleoside analogue 64a-d. This reaction involves nucleophilic dislpacemnt of the anomeric hydroxyl group which activated by Lewis acid catalysis. On the other hand condensation of 63 with D-glucose in sodium carbonate as basic catalyst instead of Lewis acid afforded the bis- quinclidine sugar 65. In addition the Mannich base analogue 66 was synthesized by treatment of 63 with glucose and morpholine under Mannich reaction condition(Scheme 14). [19,].



Scheme 14. Construction of acyclic C-nucleosides **64-66**

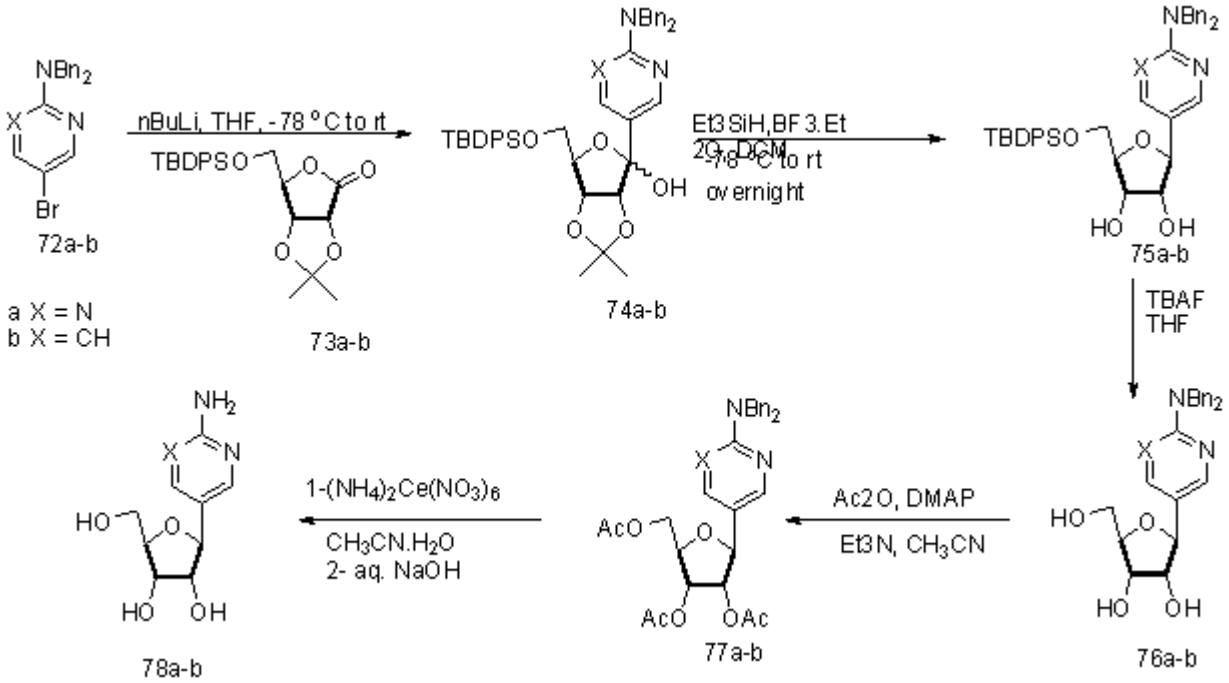
Coupling of aryl or hetroaryl lithium reactants to protected sugar lactone gave hemiketal intermediate, which subsequent steroselective reduction afforded the desired C-nucleoside with high β stereoselectivity. Thus, lithiating bromoheterocycle **67** using n-butyl lithium at -78 °C afforded the lithio species *in situ* which reacted with the protected lactone **68** to generate the hemiaketal **69**. Subsequent anomeric reduction using triethylsilane and boron trifluoride etherate furnished **70**. Metobo et. al. explain the steroselectivity to β -anomer on the basis that the chelation of silicon to either 2\- or 3\-benzyl ether oxygen electron pair results in delivery of hydride anion from a favored face to furnish only the β-anomer or almost exclusively (Scheme 15). [20,].



67 68 69 70 71

Scheme 15. Reaction of heteroaryl lithium with sugar lactone to prepare **71**

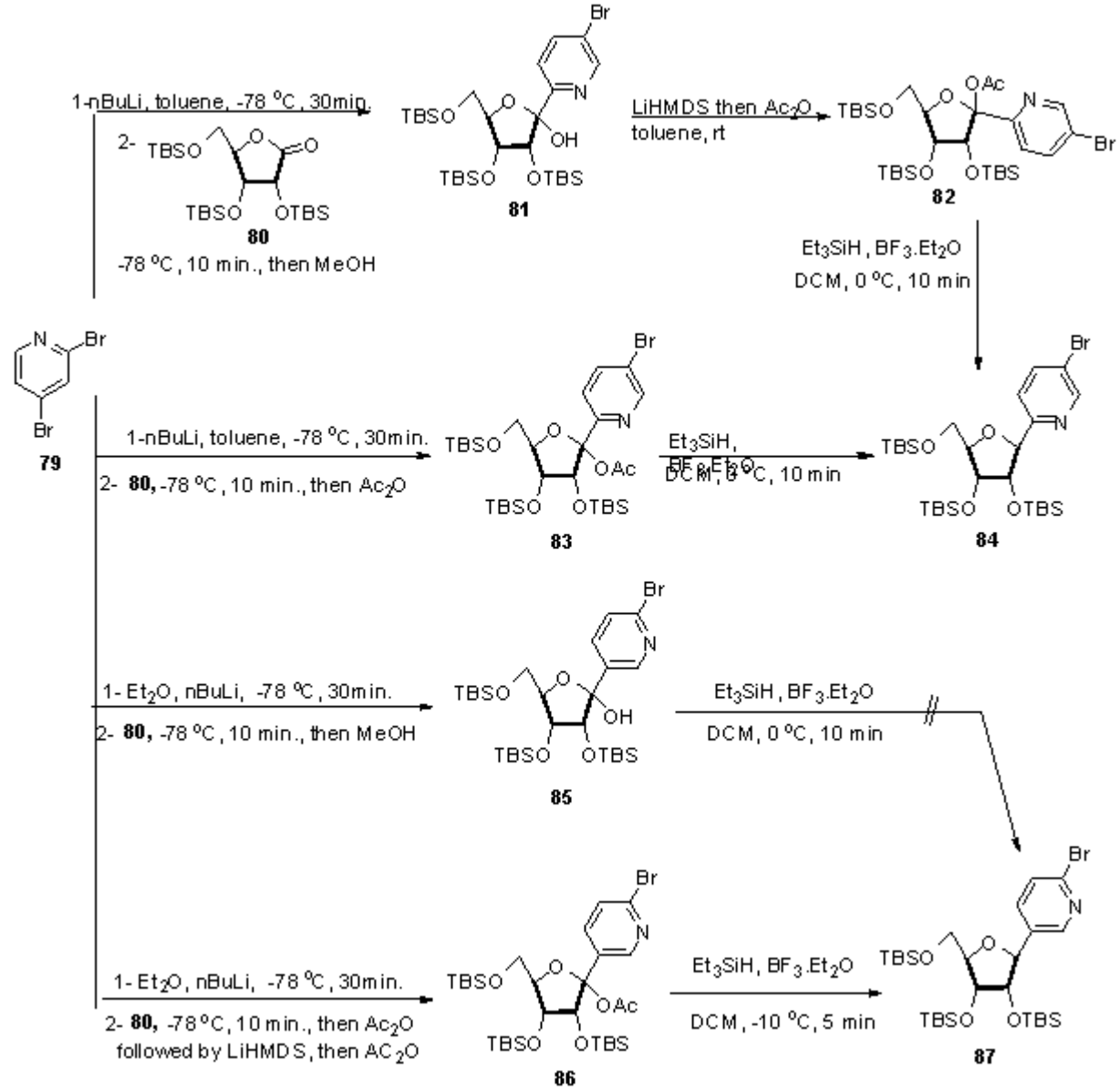
C- ribononucleoside that bear amino pyrimidine **78a** or amino pyridine **78b** have been synthesized using the same synthetic approach, but it was found that protection of the amino group with benzyl bromide are more suitable for coupling with the sugar component. Also it was found that the dehydroxylation of hemiketal intermediate **74a-b** with Et_3SiH in presence of strong Lewis acid led to removal of the 2,3-O-isopropylidine group affording the corresponding C-nucleoside (Scheme 16). [21,].



72a-b 73a-b 74a-b 75a-b 76a-b 77a-b 78a-b

Scheme 16. Reaction of heteroaryl lithium with sugar lactone to prepare C-nucleosides **76**

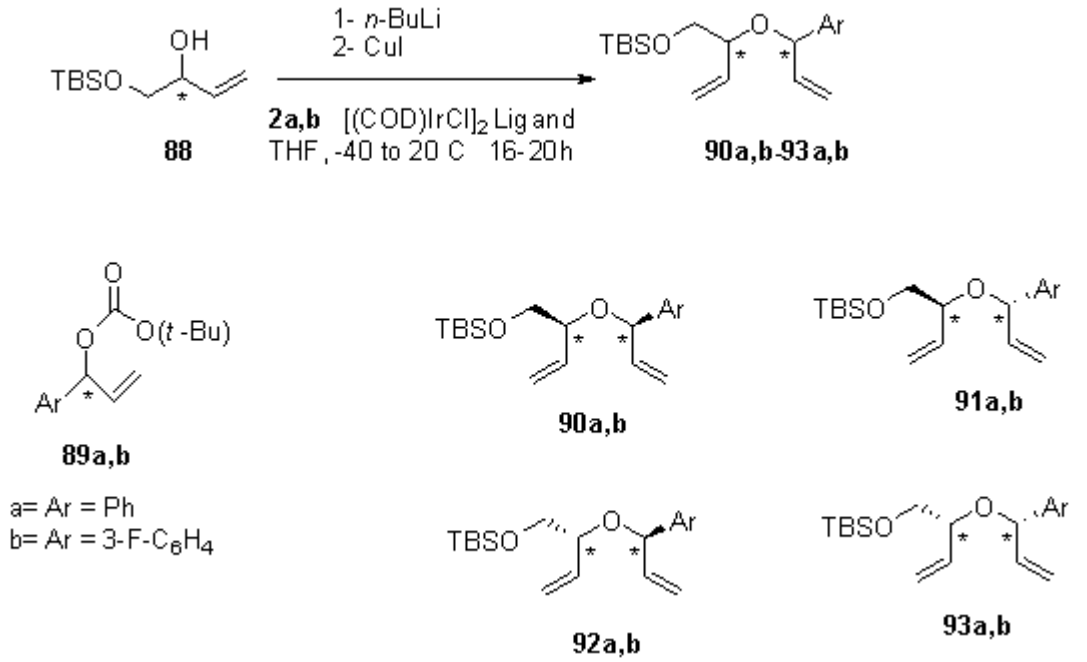
The synthesis of 5-bromopyridin-2-yl and 6-bromopyri -din-3-yl C-ribonucleosides was based on the regioselective lithiation of 2,5-dibromopyridine **79**. In toluene the lithiation proceeded at position 2 leading to 5-bromo-2-lithiopyridine, whereas in Et_2O the lithiation took place at position 5 to furnish 2-bromo-5-lithiopyridine (Scheme 17).



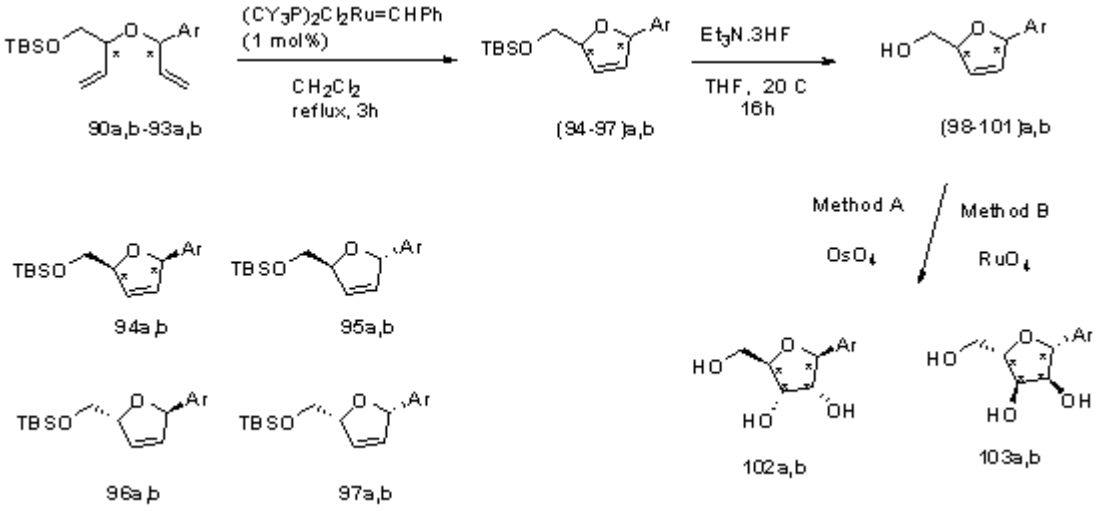
Scheme 17. Synthetic approachs to C-nucleosides **84** and **87** from 2,4-dibromopyridine

4. Construction of the Spacer on the Base

A stereo-controlled synthesis *via* allylic substitution and ring closing metathesis sequence was reported to construct the sugar moiety of some aryl C-Nucleosde 108a-c. Where as the reaction of the enantiopure alcohol **88** with the enantiopure branched carbonated compounds **89a,b** in presence of Ir(I) catalyst [23, ,] afforded the respective enantiopure products **90-93** in good yields (Scheme 18). Ring closing metathesis of the bisallyl ethers **90-93** in presence of a catalyst led to the formation of the desired 1,5-dihydrofuran derivatives **94a,b-97a,b** which were deprotected by treatment with $Et_3N.HF$ to afford the corresponding alcohols **98a,b-101a,b** (Scheme 19). Also vicinal dihydroxylation of the isolated cis-dihydrofuran derivatives **94a,b** and **97a,b** using either osmium tetroxide or ruthenium tetroxide as catalysts were performed to obtain compounds **102a,b** and **103a,b** in excellent yield.

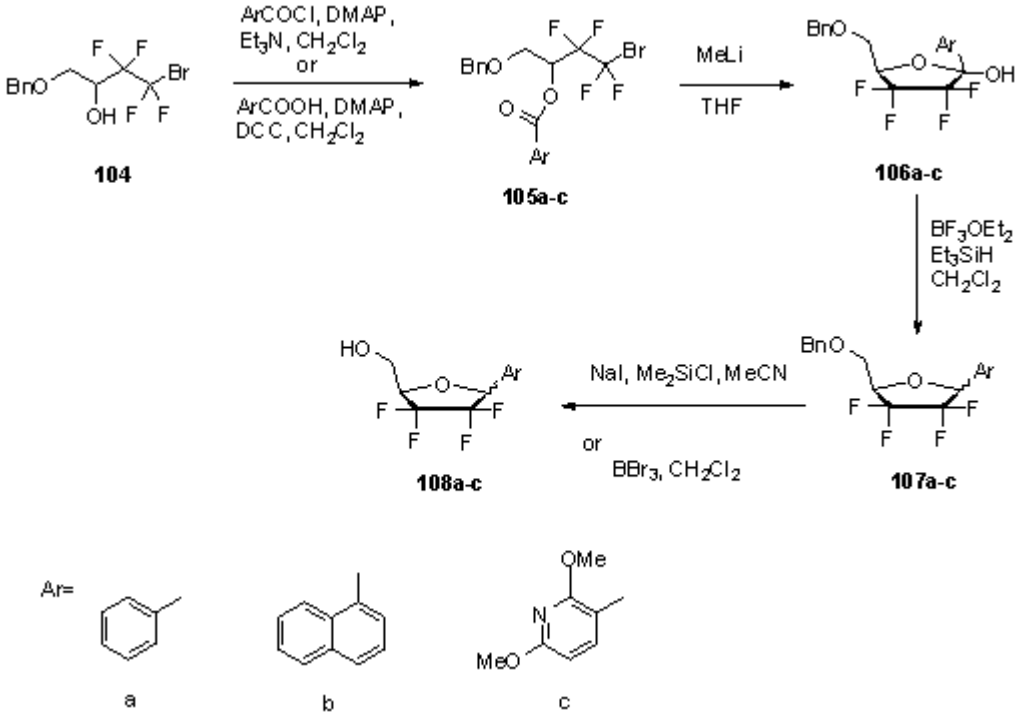


Scheme 18. Preparation of bisallyl ethers **90-93**



Scheme 19. Synthetic approaches to C-nucleosides **102** and **103** via ring closing metathesis sequence of bisallyl ethers

Esterification of the tetrafluorinated alcohol **104** followed by cyclization and dehydroxylation was performed to yield the aryl C-nucleoside derivatives **108a-c** (Scheme 20). [24, ] Thus, esterification of **104** using either acyl chlorides in CH_2Cl_2 in presence of Et_3N and 4-dimethylaminopyridine (DMAP), or carboxylic acids, which was performed in CH_2Cl_2 in presence of DCC and DMAP gave the desired esters **105a-c** in good yields. The obtained esters are then cyclised using MeLi in THF to obtain the cyclised lactols **106a-c** which underwent reductive dehydroxylation to give the protected derivatives **107a-c** followed by debenzylation using either NaI in Me_3SiCl and MeCN or BBr_3 in CH_2Cl_2 to obtain aryl C-nucleoside derivatives **108a-c**.



Scheme 20. Synthetic approach to fluorinated C-nucleosides **108**

5. Transformation of the Existing C-nucleosides to Another Ones

Commonly transformation of the C-nucleosides to other ones is carried out to improve the biological activity of the existing C-nucleosides without breaking the C-C bond between both the sugar and the base moieties.

Modification of the existing C-nucleosides occurred either in the sugar or base parts of the existing natural or synthetic C-nucleosides.

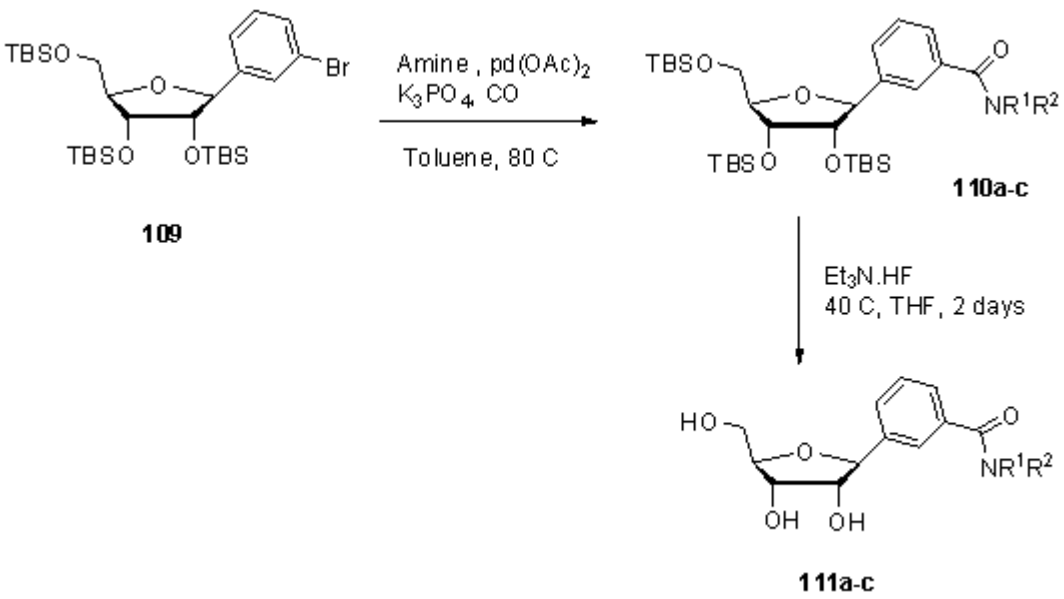
5.1. Modifications on the Base Moiety

Modifications on the heteroaryl (aryl)-C-nucleosides using organometallic catalysis were reported. In 2009 Hocek et. al. described the aminocarbolylation of bromophenyl-C-ribonucleoside **109** with CO (1 atm) with different amines in presence of lead acetate, xantphos and potassium phosphate in toluene to give the corresponding amides **110a-c** (Scheme 21, Table 1). [25,] Deprotection of the silylated nucleosides **110a-c** using $Et_3N.3HF$ at 40°C for two days followed by treatment with K_2CO_3 led to the formation of the desired free C-ribonucleosides **111a-c**. Benzamide-C-ribonucleosides were found to have a biological character as to be a strong cytostatic agent including apoptosis in cancer cells.

The unprotected 5-bromofuran-C-nucleoside **112** was used as a potential intermediate for aqueous phase cross coupling reactions. The Suzuki-Miyaura cross coupling reaction of this compound with different aryl boronic acids carried out in presence of lead acetate, tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) ligand and Cs_2CO_3 as a base for 4h at 120°C yielded the biaryl β-C-nucleosides **113a-g** (Scheme 22). [26,] These nucleosides have high fluorescence properties that can be used as fluorescent labeling in biomolecules.

5.2. Modifications in the Spacer Part

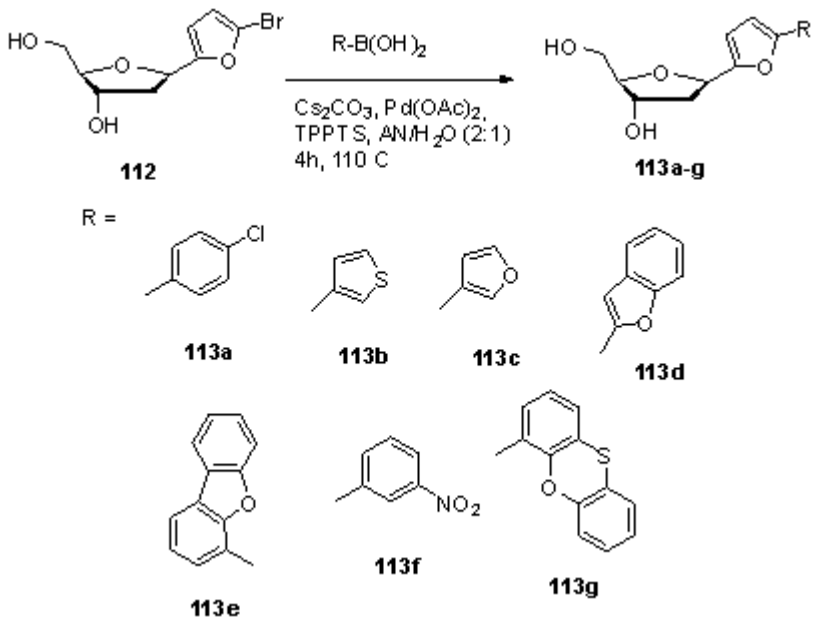
The conversion of compounds **114** and **115** into the hitherto unknown 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydro- C-nucleosides **116**, **117**, **118** and **119** was performed (Scheme 23) [27, , , ,]. These compounds were evaluated in a cell-based assay against Human immunodeficiency 1 (HIV-1). Protection of the 5'-hydroxyl group in **114** and **115** using tert-butyldimethylsilyl chloride and imidazole in anhydrous dimethylformamide or pyridine gave **116** and **117** respectively. The 4-thione product was converted to the 4-methylthio derivative **118** using methyl iodide in aqueous sodium hydroxide. Compounds **116** and **118** were then converted into 1,3-dioxalane-2-thione derivatives **119** and **120** followed by heating in presence of triethylphosphite to yield **121** and **122**. Deprotection of these products in presence of tetrabutylammonium fluoride gave the 2',3'-dideoxy-2',3'-didehydro-C-nucleosides **123** and **124**. Compound **124** reacts with ammonia in methanol at 120ºC under microwave to yield the amino derivative **125**. Finally, hydrogenation of **123** and **125** using catalytic amount of Pd/C in ethanol yielded 2',3'-dideoxy-C-nucleosides **126** and **127**.



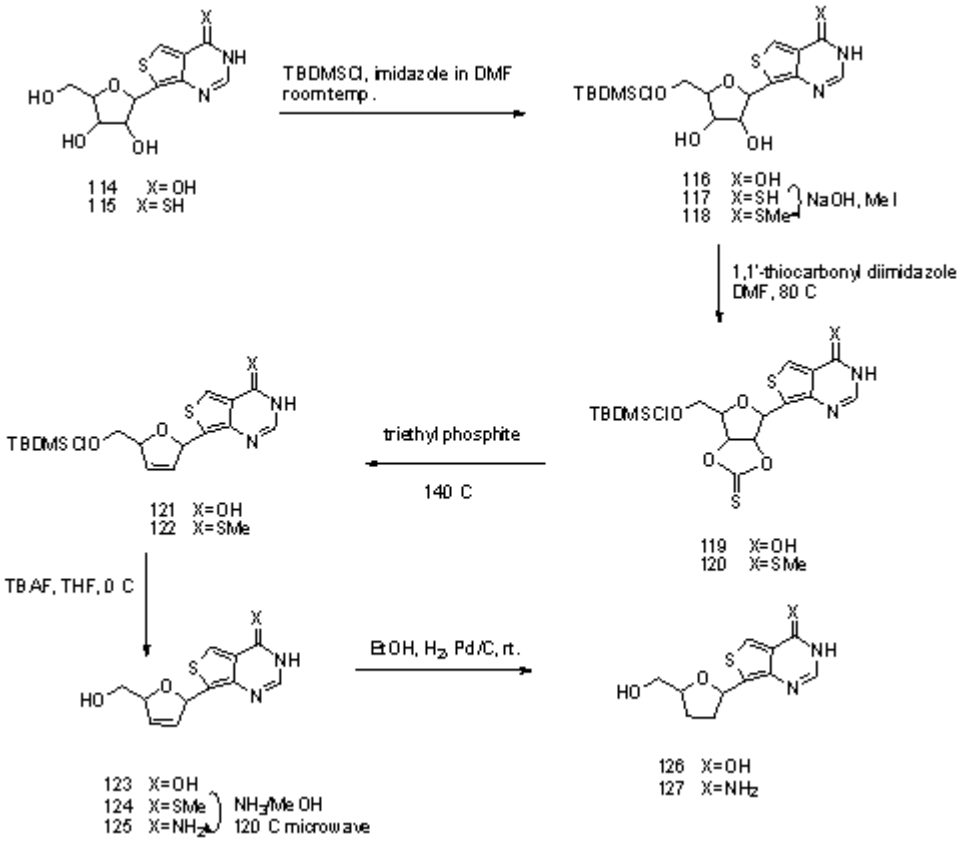
Scheme 21. Chemical reactions of modification to C-nucleosides **111**

Table 1. Aminocarbonylation of 3-bromophenyl-C-ribofuranoside

Entry	Amine	R^1	R^2
a	HN	$-(CH_2)_4-$	
b	HN	$-(CH_2)_5-$	
c	HN O	$-(CH_2)_2O(CH_2)_2-$	

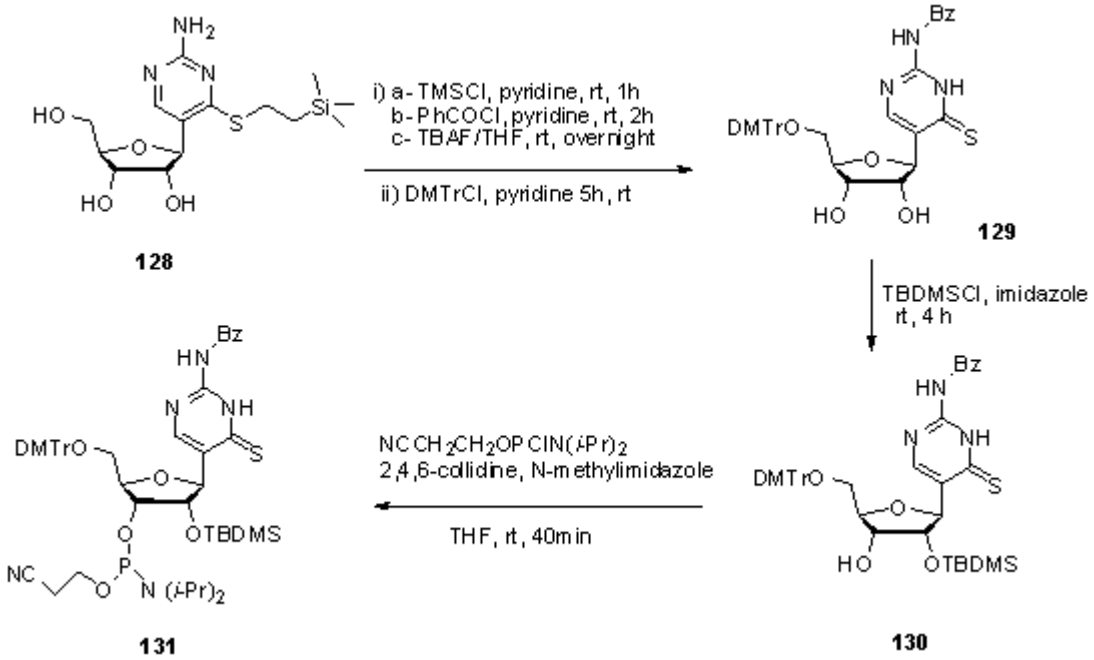


Scheme 22. Suzuki-Miyaura cross coupling reaction to prepare C-nucleosides **113**



Scheme 23. Synthetic modification of C-nucleosides **114-115** to **126-127**

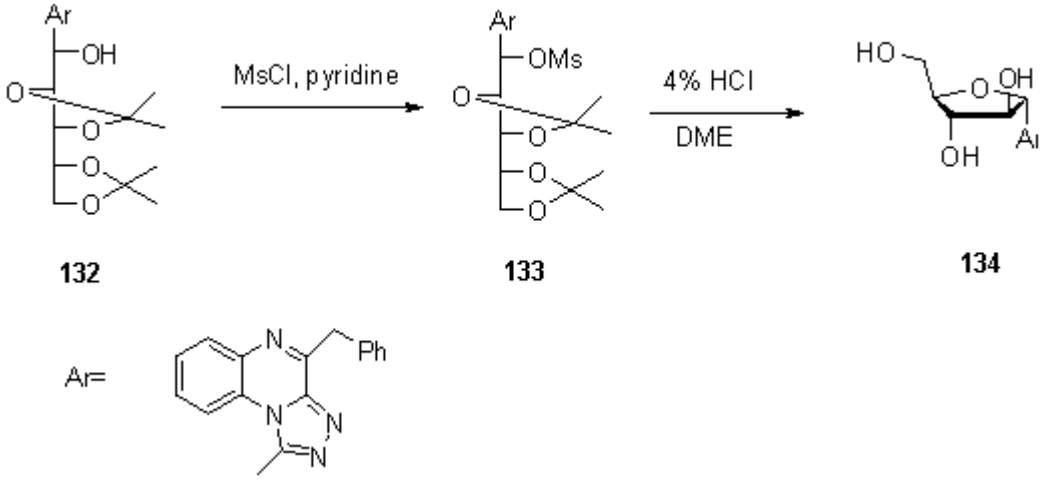
In order to incorporate $s^4\psi iC$ into triplex forming oligonucleotides [28,], S.-Q. Cao et al synthesized 3'-phosphoramidite derivative **131** starting from **128** (Scheme 24). There **128** was treated with 1.0 M tetrabutylammonium fluoride in THF followed by protecting the 5'-OH group using DMTr to give **129** in good yield. The 2'-OH protected derivative **130** was obtained by action of TBDMSCl on **129**. Finally the reaction of **120** with $NCCH_2CH_2OPClN(i\text{-}Pr)_2$ in presence of 2,4,6-collidine and N-methylimidazole gave the phosphoramidite **131**.



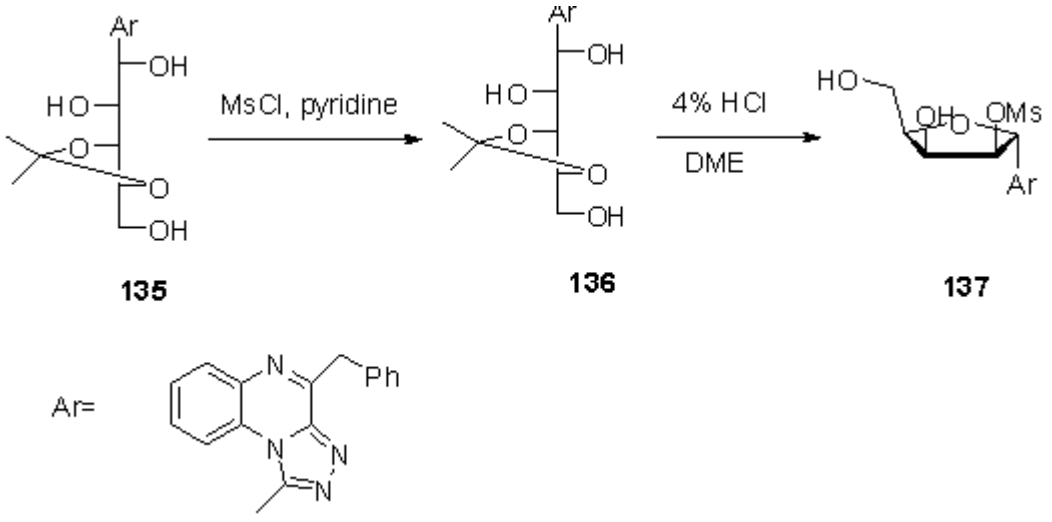
Scheme 24. Synthetic modification of C-nucleoside **128** to **131**

5.3. Cyclization of the Acyclic Analogue

Transformation of the di-*O*-isopropylidine acyclic C-nucleoside compound **132** to its *O*-mesyl derivative **133** was performed [29,] by addition of methansulfonyl chloride in pyridine at 0°C for 3 h, followed by deprotection and cyclization to yield the desired cyclic C-nucleoside **134** in good yield by refluxing compound **133** using 4% HCl in 1,2-dimethoxyethane (Scheme 25). The selective cyclization (C-4'-C'-1) and the configuration were confirmed using ^{13}C-NMR and the nuclear overhauser effect (NOE) experiment. Similarly, the isopropylidine derivative **135** was transformed to the cyclic compound **137** under the same conditions through the formation of the tri-*O*-mesylated derivative **136** (Scheme 26).

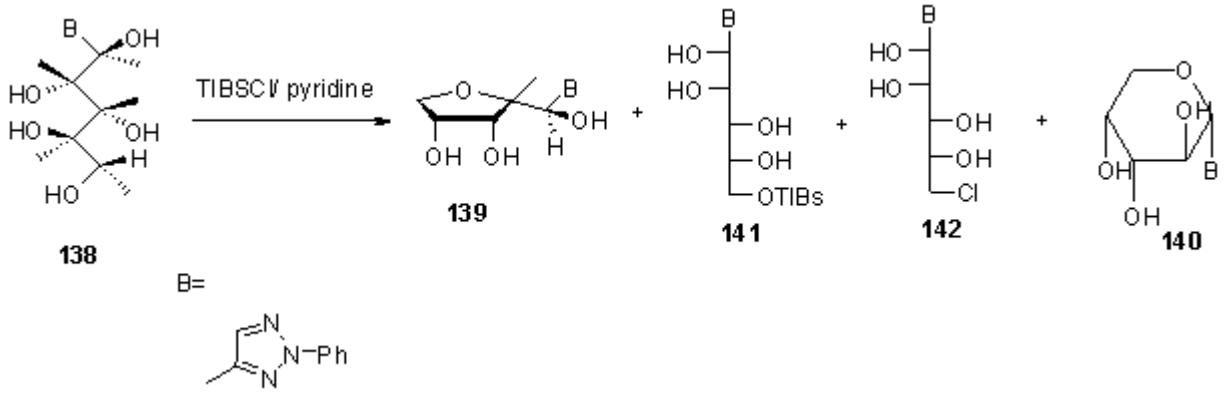


Scheme 25. Ring closure steps of acyclic C-nucleoside **132** to the cyclic **134**



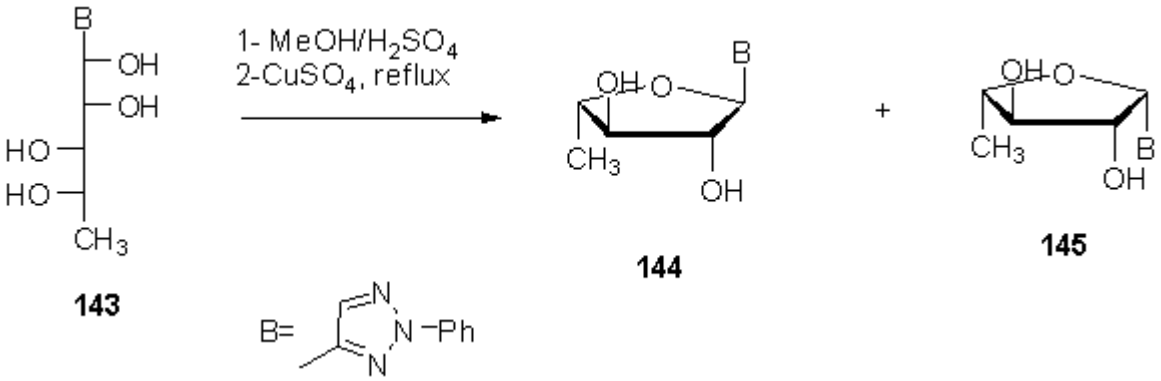
Scheme 26. Ring closure steps of acyclic C-nucleoside **135** to the cyclic **137**

The reaction of the acyclic C-nucleoside **138** with 2,4,6-tri-isopropylbenzenesulfonyl chloride (TIBSCl) in pyridine gave the homo-C-nucleoside derivative 4-(2,5-anhydro-D-*manno*-pentitol-1-yl)-2-pheny-2*H*-1,2,3-triazole (Scheme 27) **139** [30,], where region-selectivity will occur due to the bulkiness of (TIBSCl). This dehydrative cyclization under basic conditions also yields a minor thermodynamically product **140** as a result of the 1,5-S_N^2 cyclization. During this reaction the intermediate **141** and the byproduct **142** were isolated from the reaction mixture.



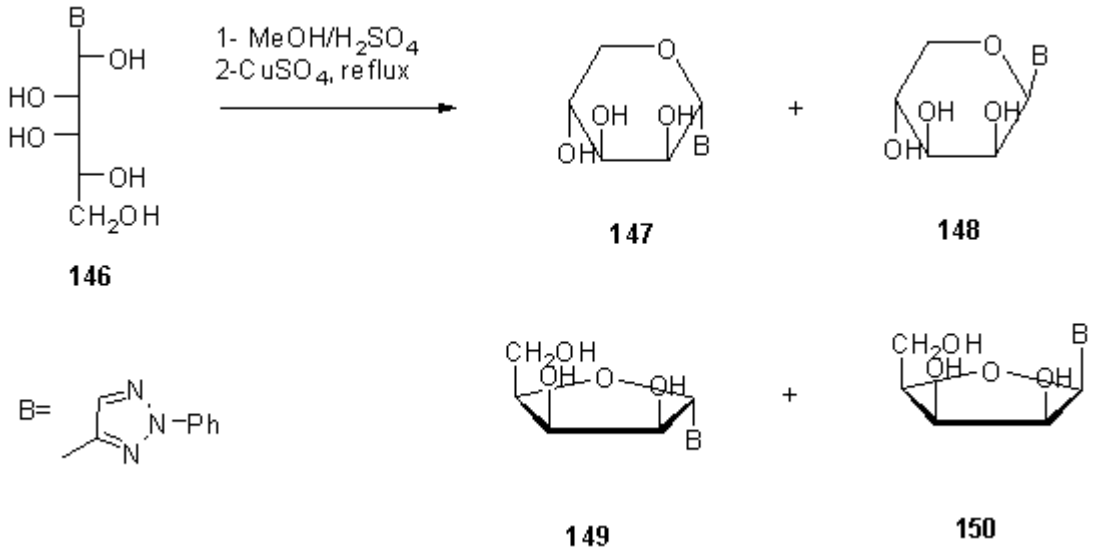
Scheme 27. Ring closure steps of acyclic C-nucleoside **138** to the cyclic **139-140**

Synthesis of 4-(5-deoxy-α- and β-L-arabinofuranosyl) -2-phenyl-2*H*-1,2,3-triazoles **144** and **145** were performed [31,] and the anomeric configuration were determined by the CD and NMR spectroscopic measurements (Scheme 28). Acyclic 5-deoxy-L-*manno*-pentitol-1-yl nucleoside **143** was treated with methanolic sulfuric acid and subsequent reflux with copper sulphate yield the anomeric mixture of **144** and **145,** which were separated by chromatography.



Scheme 28. Ring closure steps of acyclic C-nucleoside **143** to the cyclic **144-145**

Similarly, the dehydrative cyclization of 4-(D-*galacto*-pentitol-1-yl)-2-phenyl-2H-1,2,3-triazole **146** catalyzed by acid gave the anomeric α,β-D-lyxopyranosyl and furanosyl derivatives **147-150** (Scheme29). [32,]

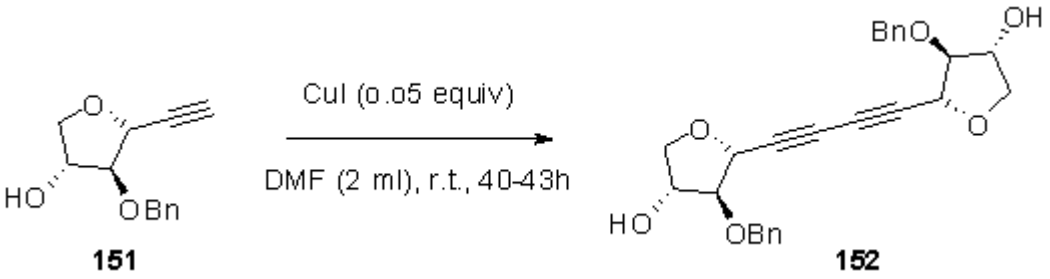


Scheme 29. Dehydrative cyclization of acyclic C-nucleoside **146** to **147-150**

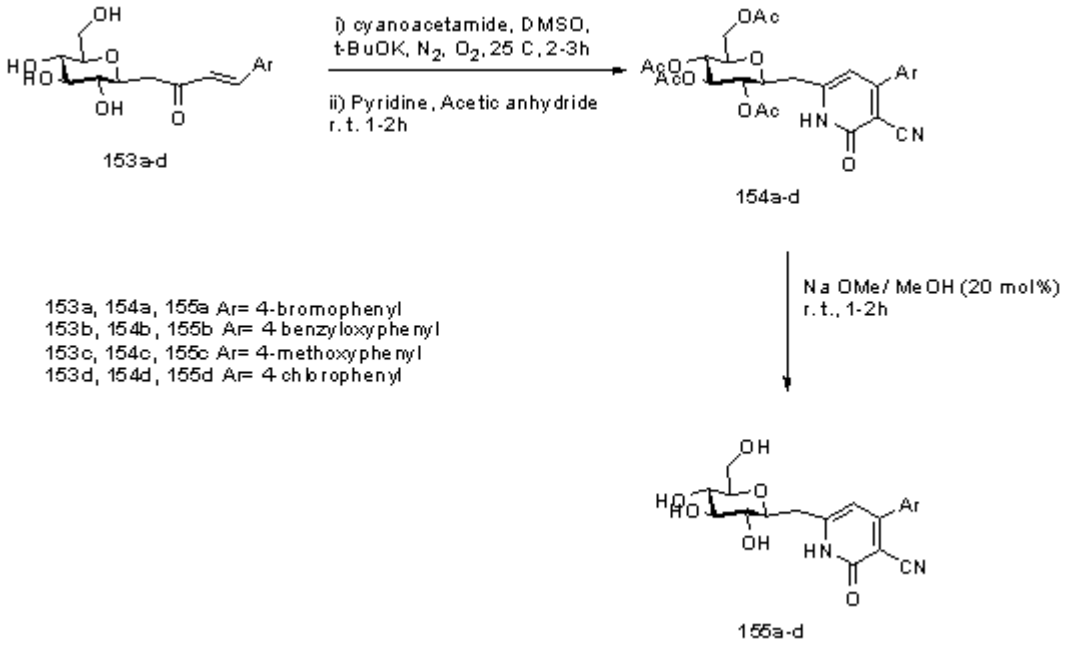
6. Miscellaneous Synthesis

The homo-coupled product **152** was obtained from the reaction of THF-alkyne **151** with different catalytic systems in dry DMF in order to obtain the optimized reaction conditions such as i) CuI, $CsCO_3$ and NaI, ii) CuI and $CsCO_3$ and iii)CuI only, to give the desired product in good yields. It was found that both $CsCO_3$ and NaI have no effect in the reaction (Scheme 30). [33,]

The reaction of butenonyl C-glycosides with cyanoacetamide via Micheal addition followed by dehydrative cyclization and oxidative aromatization gave the corresponding glycosyl pyridines. These compounds are evaluated for their antidiabetic potential in vitro. (*E*)-1-(β-D-glucopyranosyl)-4-(aryl)but-3-en-2-ones **153a-c** reacted with cyanoacetamide in DMSO, t-BuOK, N_2 and O_2 at room temperature followed by acetylation to give the respective 3-cyano-4-(aryl)-6-[(2'',3'',4'',6''-tetra -*O*-acetyl -β-D-glucopyranosyl)methyl]pyridones **154a-c** in good yields. Subsequently, deacetylation of these compounds with NaOMe/MeOH afforded the corresponding 3-cyano-4-(aryl)-6-[(β-D-glucopyranosyl) methyl]pyridones **155a-c** (Scheme 31). [34,]



Scheme 30. C-C coupling reaction of **151** to C-nucleoside **152**



Scheme 31. Synthetic steps to build up the heterocyclic base on **153-155**

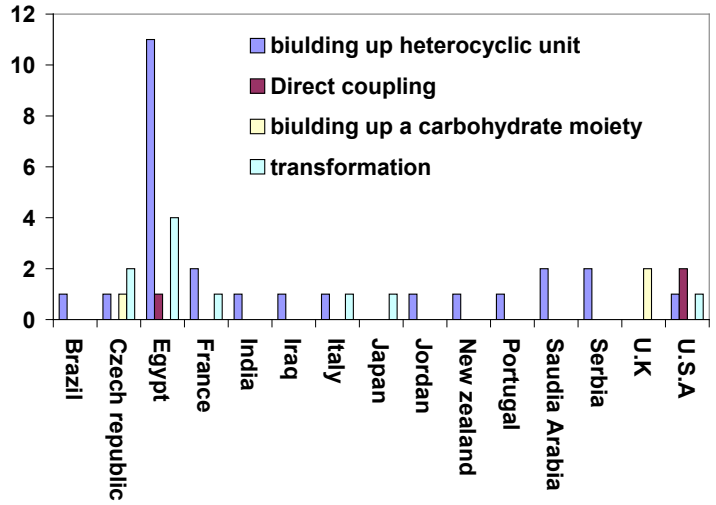


Figure 2. Distribution of C-nucleosides synthetic tactics by countries

7. Conclusions

This work highlights a recent progress in developmental strategies to build up C-nucleosides and analogues. It does not attempt to be comprehensive in particular, it intended to spot locations of work and synthetic tactics (Figure 2), then correlate that to international *vs*. national transformation of methodologies. From the Middle East, choosing Egypt as a model, it is clear that the internal transformation of research perspectives there dominates. However, science diplomacy may provide a forum for international collaborative research, which leads to intriguing topics of potential applications for sustainable developments

Dedicated to the memory of Prof. Hans W. Zimmer[1]

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[1] Prof. Hans Willi Zimmer (1921-2001) had served at University of Cincinnati (Ohio, USA) for 47 years and arranged for a student exchange program with the University of Stuttgart (Germany) in the early eighties. In keeping with the spirit of international exchange, which Hans initiated, Hans and Marlies Zimmer International Scholar Fund was endowed in his memory.

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