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AN OVERVIEW OF VARIOUS APPROACHES FOR THE SYNTHESIS OF 1, 2-DIDEOXY-β-ARYL OR HETEROARYL-*D*-RIBO- FURANOSE FRAMEWORK

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The present review has summarized the various approaches available in the literature to arrive at 2-deoxy-*C*-aryl or *C*-heteroaryl-nucleosides. Essentially there are two main approaches. The first one involves the use Heck type palladium-mediated cross coupling reactions (PMCCR) for the C-C bond formation between the anomeric carbon of ribofuranoid glycals and the iodoaromatics or iodoheterocycles. In the more prevalent and second approach, the aryl or heteroaryl –organometallics reacts with suitably protected 2-deoxy-*D*-ribose for the formation of C-C bond at the anomeric position. The protected 2-deoxy-*D*-ribose or derivatives can be classified into three categories. First category includes protected 2-deoxy-*D* -ribose sugar in the *furanose* form and amongst them the 1-chloro derivative has been very popular. Second category represents the differentially protected 2-deoxy-*D* -ribose in the *acyclic* form. The last category includes the protected 2-deoxy-*D*-ribose in the higher oxidation stage, in the *lactone* form. The choice of the derivative used in a particular synthesis solely depends on the target compound to be synthesized and the convenience of the functional group manipulation therein. Barring low yields, Woski's protocol of reacting 3,5-diprotected 2-deoxyribonolactone with lithiated aromatics stands out distinctly with regard to simplicity and convenience for rapidly arriving at 2-deoxy-*C*-aryl-nucleosides. Our own approach based on *Umpolung* concept and which involves the use of readily available α-aminonitriles as arylacyl anion equivalents for coupling with differentially protected bromo-derivative of erythritol as electrophile, holds significant promise.

Key Words: 1,2-dideoxy-1-aryl-*D*–ribofuranoses; 2-deoxy-*C*-aryl-nucleosides; 2-deoxy-*C*-nucleosides; *C*-nucleosides ribofuranoidglycal; C-nucleobase

1 Introduction

Natural nucleosides are *N*-glycosides of the general structure **1**, wherein a heterocyclic aglycon and a sugar, *D*-ribose or 2-deoxy *D*-ribose, are linked to each other by a carbon-nitrogen bond. The aglycon part is either pyimidine or purine type heteroaromatic bases. *C*-nucleosides are molecules in which the aglycon part, aryl or heteroaryl ring is connected through carbon-carbon bond. It is their close resemblance to the natural nucleosides which gave compounds of the type **2** their common name "*C*-nucleosides" (Fig. 1). The enhanced stability of the C-C bond against C-N bond is responsible for the resistance of *C*-nucleosides towards hydrolytic and enzymatic cleavage and thereby confers one of the important reasons for their growing utility and significance. Naturally occurring *C*-nucleosides have been antibiotics[1], displayed anticancer and/or antiviral activity and chemotherapeutic properties.[1,2] The synthetic 2-deoxy-*C*-aryl, **3** or heteroaryl nucleosides in particular have been building blocks for incorporation into artificial DNA and RNA synthesis for the control of gene expression. 2-deoxy-*C*-aryl-nucleosides are gaining prominence as excellent probes for understanding the electronic and steric factors involved during recognition phenomenon on DNA strand. Non-polar 2-deoxy-*C*-aryl-nucleosides[3] in particular have been the best probes towards the understanding of electronic effects because they maintain the size and shape of the natural nucleosides and relinquish the Watson-Crick hydrogen bonding aspect while another set of 2-deoxy-*C*-aryl-nucleosides with gradually increasing size have served as "molecular rulers" for gaining deeper insight into the steric effects.[4]

From a synthetic point of view a very large number of synthetic approaches have been explored for *C*-nucleosides.[5a] However, less attention has been focused on their 2-deoxy analogues, although

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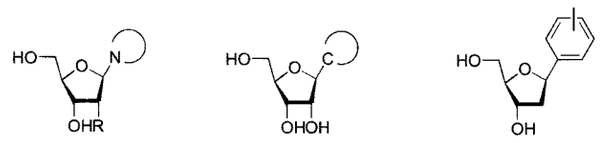


1 NATURAL NUCLEOSIDES
R = OH: ribo nucleosides
R = H: 2-deoxy ribo nucleosides

2 C-NUCLEOSIDES

3 2-DEOXY-C-ARYL-NUCLEOSIDES

Fig. 1

2′-deoxygenation using radical based Barton McCombie reaction[5b] affords the same by an extra synthetic step in the scheme for *C*-ribofuranosides.[5c]

2 Methods for Construction of 2′-deoxy-aryl or Heteroaryl-*C*-nucleosides

The present review focuses on delineating various routes scattered in the literature to arrive at 2′-deoxy-aryl or heteroaryl-*C*-nucleosides directly and not invoking the above deoxygenation scheme via ribofuranosides. Direct attachment at C-1 of aglycon, aryl or heteroaryl unit to suitably protected 2′-deoxyribose derivative forms the basic principle of the two main approaches presently used to arrive at the target of 2-deoxy-*C*-aryl or *C*-heteroaryl-nucleosides. The disconnection and the resulting synthetic equivalents are shown in Fig. 2.

3 Strategy Based on Heck Type Coupling

Dave and co-workers carried out the pioneering work in employing Heck type palladium-mediated cross coupling reactions (PMCCR) for the C-C bond formation between the anomeric carbon of ribofuranoid glycals (1,4-anhydro-2-deoxy-*D* -erythro-pent-1-enitol) and the iodoheterocycles.[6,7] It was their initial palladium mediated coupling of ribofuranoid **4** with dihydropyrimidin-5-yl-mercuric acetate **5**, which led to subsequent studies towards this approach of synthesizing 2-deoxy-*C*-heteroaryl-nucleosides framework (**Scheme 1**).

The parent unprotected ribofuranoid glycal **4** in which both the hydroxyls at C-3 and C-5 are free, the palladium mediated coupling with aglycon yielded a mixture of α- and β-*C*-glycosides owing to competitive attack of the intermediate organopalladium reagent on both the faces of the glycal ring.[8] The stereochemistry at the anomeric carbon in the initial adduct from PMCCR and hence in the final product could be effectively controlled by incorporating suitable protecting groups at the C-3 and C-5 hydroxy functions in the ribofuranoid glycal. [8,9] For the desired β-configured 2-deoxy-*C*-glycosides, protection of the C-3-hydroxyl group by a bulky group could offer a valuable stereo-

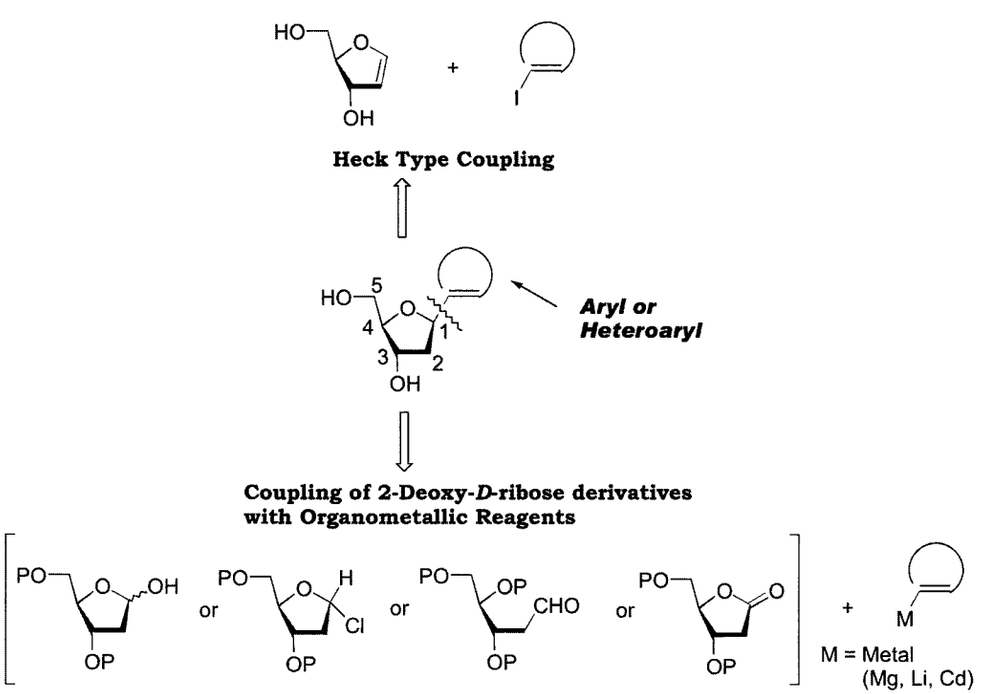
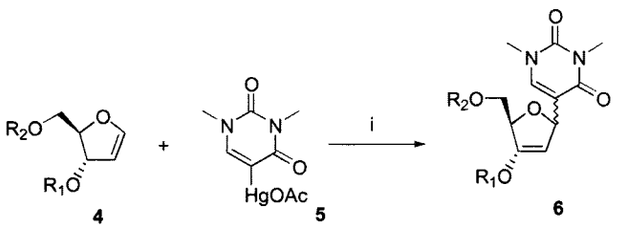


Fig. 2



4 : $R_1 = R_2 = H$
4a: R_1 = TBDPS, $R_2 = H$

(i) $Pd(OAc)_2$, acetonitrile, r.t.

Scheme 1

direction. In this context, ribofuranoid **4a** has become significantly important because the silyl ether protection can be easily removed after it has offered the stereo-directing effect in the PMCCR.[10] Although a variety of iodoheterocycles **7-14**, from various classes of heterocycles and briefly represented in Fig. 3 have been successfully coupled with ribofuranoid **4a** in particular, the approach had some limitations at the initial stages due to limited accessibility of the ribofuranoid glycals.

In contrast to pyranoid glycals which are readily obtained, the furanoid glycals are scarce and also highly acid labile. Ireland's four step procedure,[11] **(Scheme 2)** starting from 2, 3-isopropylidene-protected *D*-ribonolactone **15** and with an impressive overall yield of 60%, had some difficulties in scale-up due to aluminum hydride reduction, chlorination and dissolving metal reduction required in this route.

Pedersen[12] later developed a highly convenient and simple two-step procedure for the un-protected parent ribofuranoid glycal **4** from cheap and commercially available thymidine **20**, (R = R_1 = H). The scope of this procedure was successfully

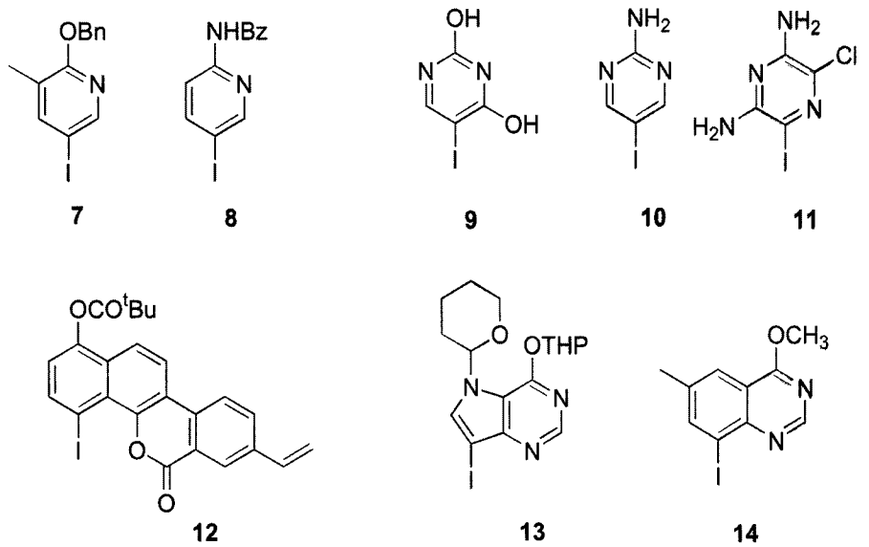
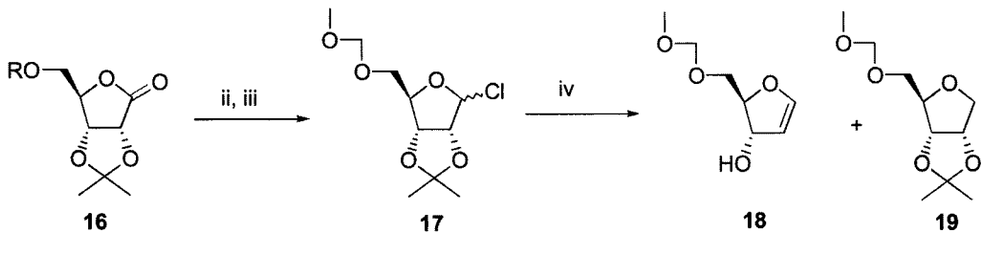


Fig. 3

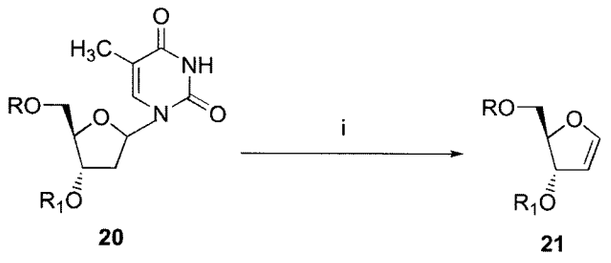


i ⌐ **15** R=H
└→ **16** R=CH_2OCH_3

(i) $ClCH_2OCH_3$, $C_2H_5N(i\text{-}C_3H_7)_2$; (ii) DIBAL, Et_2O, -78°C; (iii) Ph_3P,CCl_4, THF; (iv) Excess Li-NH_3

Scheme 2

Starting thymidine	Ribo-	R furanoid	R_1 (%)	Yield
20a	**4a**	H	TBDPS	79
20b	4	H	H	80
20c	21c	TBDMS	H	74
20d	21d	TBDPS	H	91
20e	21e	Tol	H	52
20f	21f	TBDMS	TBDMS	69
20g	21g	TBDPS	TBDPS	80
20h	21h	TBDMS	TBDPS	79
20i	21i	TBDPS	TBDMS	59
20j	21j	Tol	TBDMS	74
20k	21k	Tol	TBDPS	94
20l	21l	H	TBDMS	36



20 **21**

(i) HMDS, $(NH_4)_2SO_4$, reflux

Scheme 3

expanded by Hammer *et al.* [13] by the way of incorporating varied protections at C-3 and C-5 hydroxyl and arriving at multi-gram quantities of the glycals (**Scheme 3**).

The 3, 5-bisprotected ribofuranoid glycals **21a-c** have also been conveniently obtained by an E2 elimination process on the sulfonate esters under basic conditions,[14] however the approach is lengthy and starts with relatively expensive 2-deoxy-*D*-ribose as the starting material (**Scheme 4**).

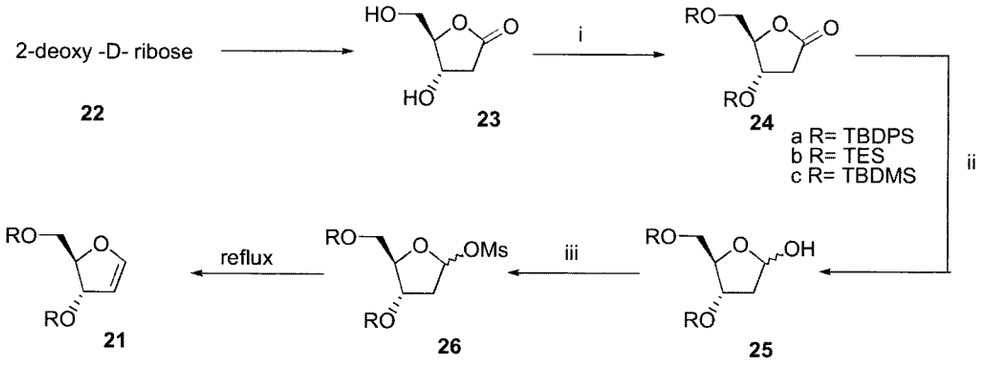
In a yet another and less used approach, Kassou and Castillon[15] have accessed the ribofuranoid glycals carrying acyl protections at C-3 and C-5 hydroxys in particular, through selenoxide based elimination (**Scheme 5**).

With the availability of the differently protected ribofuranoid glycals, the Heck type coupling approach to 2-deoxy-*C*-aryl-nucleosides is becoming common. Very recently Kool *et al.*[16] have used the above strategy based Heck type coupling for the synthesis of **33**, benzo-fused variant of thymidine nucleoside. The key step involved coupling of the iodo-heterocycle **30** with ribofuranoid derivative **4a** under the influence of $Pd(OAc)_2/AsPh_3$. The coupled product **31** was obtained in 64% yield and subjected to de-silylation to arrive at the ketone **32**. Stereoselective reduction and deprotection afforded the target compound **33** (**Scheme 6**).

Interestingly there has been a sudden surge in the interest of unnatural L-nucleosides due to their unique potency, mechanism of action and toxicity profile. Knaus *et al*[17] used Heck type coupling to arrive at the unnatural 2-deoxy-*C*-aryl-β-L-cytidine mimics **37** by condensing L-configured ribofuranoid **34** with aryliodide **35** through the intermediate of **36** (**Scheme 7**).

4 Strategy Based on Coupling of Organometallics with 2-deoxy-*D*-ribose Derivatives

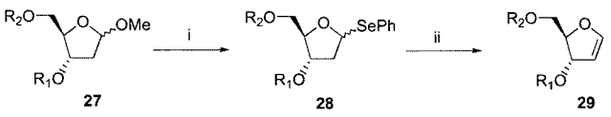
The second principal approach for 2′-deoxy-aryl or



22 **23** **24** **25** **26** **21**

(i) R-SiCl, imidazole, DMF; (ii) DIBAL, Et_2O, -78°C; (iii) Et_3N, MsCl, -50°C.

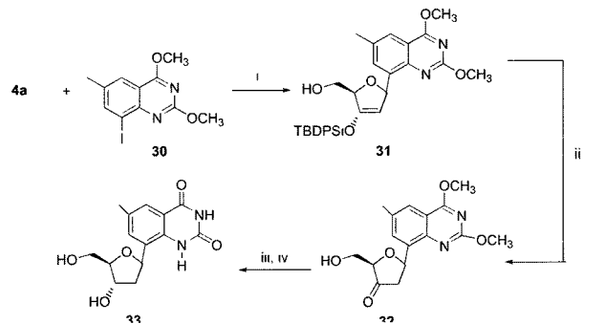
Scheme 4



a: R_1=R_2=Bn
b: R_1=R_2=pivaloyl
c: R_1=MEM, R_2=TBDPS

(i) PhSeH/BF_3.Et_2O/CH_2Cl_2, -5°C; (ii) ^tBuOOH, $^iPr_2EtN$, CH_2Cl_2, $Ti(O^iPr)_4$, 0°C.

Scheme 5



(i) $Pd(OAc)_2$, $AsPh_3$, NBu_3, 70 °C, 64%, (ii) TBAF, THF, 0°C, 84%, (iii) $NaB(OAc)_3H$, THF, AcOH, 15 °C, 93%, (iv) NaI, AcOH, 60°C, 100%

Scheme 6

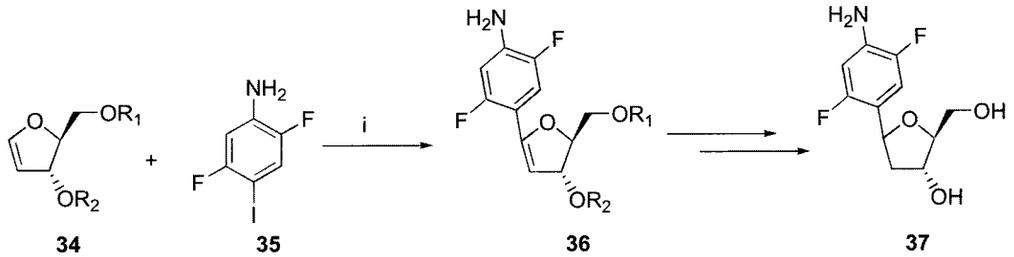
heteroaryl-*C*-nucleosides as delineated in **Fig. 2** involves the addition of aryl or heteroaryl-organometallics to 2-deoxy-*D* -ribose derivative as the required sugar electrophile. The various forms of 2-deoxy-*D* -ribose derivatives, can be classified into three categories (**Fig. 4**). First category includes protected 2-deoxy-*D* -ribose sugar in the *furanose* form **38**, **39** and the popular 1-chloro derivative **40**. Second category represents the differentially protected 2-deoxy-*D* -ribose in the *acyclic* form **41-43**. The last category includes the sugar in the higher oxidation stage and in the *lactone* form **44**, **45**. Most of these derivatives require 2-deoxy-*D* -ribose as the expensive starting material. The choice of the derivative in a particular synthesis solely depends on the target compound to be synthesized and the convenience of the functional group manipulation.

*4.1 The sugar, 2-deoxy-***D***-ribose as Electrophile in the Furanose Form*

From the category of protected 2-deoxy-*D* -ribose in the furanose form, **38** and **39** have been used. The former, 3,5-di-*O*-benzyl-2-deoxy-*D*-ribofuranose, through the 2-deoxy-*C*-alkynyl-ribofuranosides derivative **48** opens up a potential route to 2-deoxy-*C*-heterocycle nucleosides exploiting the chemistry of acetylenic functionality.[18a] Reaction of **38** with various alkynyllithium reagents afforded diastereomeric mixtures of the corresponding ring-opened alkyndiols **47**. Cobalt mediated intramolecular Nicholas reaction[18b] being reversible provided the thermodynamically more stable β-isomer (**Scheme 8**).

The other furanose derivative **39**, 3,5-*O*-(tetraisopropyldisiloxane-1,3-yl)-2-deoxy-*D*-ribofuranose easily accessible in multi-gram scale by reaction of 2-deoxy-*D* -ribose **22** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in presence of pyridine,[19] reacted with lithiated heterocycles[20a] or the corresponding zinc/cadmium salts to furnish potential precursors for the synthesis of 2-deoxy-*C*-heteroaryl-nucleosides[20b] (**Scheme 9**). Using the same furanose derivative **39**, furan and thiophene based 2-deoxy-*C*-heterocycle nucleosides, **54** and **55** respectively have been synthesized by Romesberg *et al.*[21]

The α-chlorosynthon **40**, viz 3′, 5′-di-*O*-toluoyldeoxyribofuanosyl chloride of Hofer[22] has



R_1 = *p*-Cl-Bz, R_2 = Bn

(i) $Pd(OAc)_2$, Ph_3As, Et_3N/MeCN, 57%.

Scheme 7

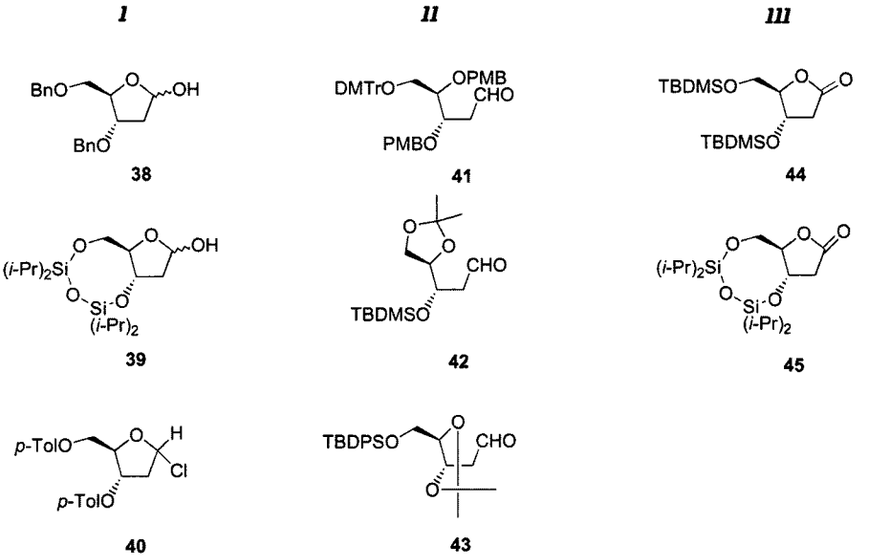
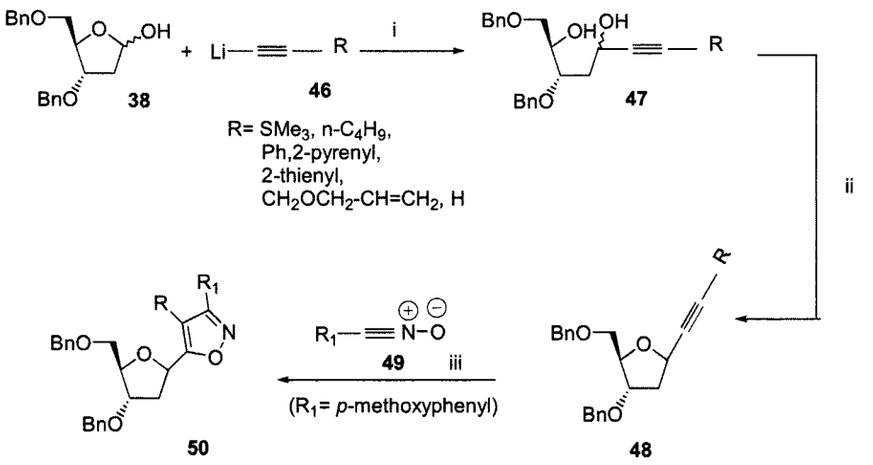
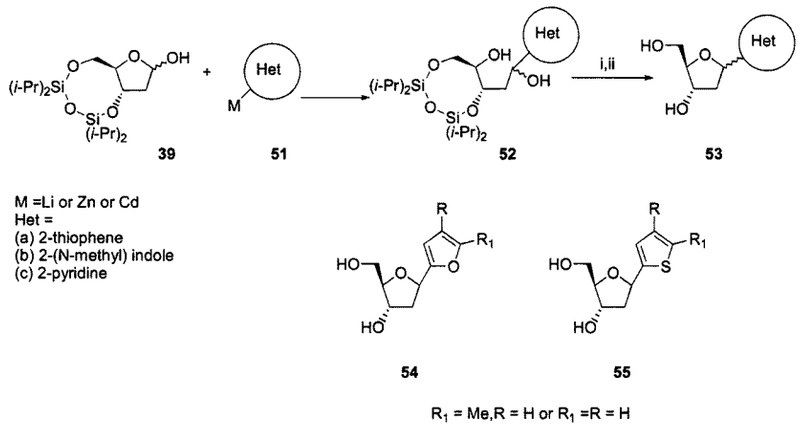


Fig. 4 Various Derivatives of 2-Deoxy-D-ribose



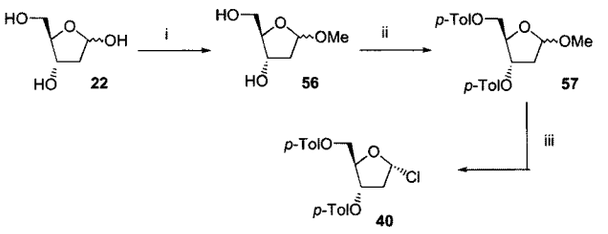
(i)THF, -20°C; (ii) a) $Co_2(CO)_8$; b) Cat TfOH; c) I_2, Et_3N; (iii) **49**,CH_2Cl_2, rt

Scheme 8



Scheme 9

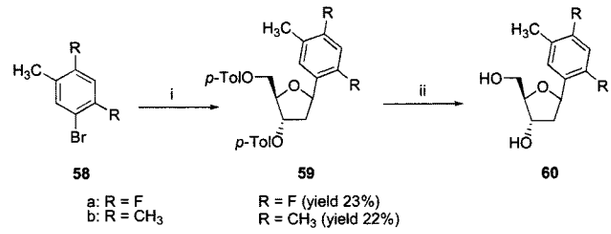
been used extensively. The a-chlorosynthon has been synthesized in three steps starting from 2-deoxy-*D* -ribose **22** as depicted in **Scheme 10**.



(i) 1% HCl in methanol; (ii) *p*-toluoyl chloride (4equiv), py; (iii) HCl gas, diethyl ether

Scheme 10

Although the first successful use of commonly available arylmagnesium halide for coupling with glycosyl halide was reported by Hurd and Bonner,[23] it was a bold initiative of Kool's group to revisit and employ this strategy to arrive at 2′-deoxy-aryl-*C*-nucleosides,[24] despite futility of the procedure also strikingly co-existed in the literature.[25] (**Scheme 11**) The product **60** was obtained, albeit in lower yields (20-25%) than reported by Hurd and Bonner[23]. The low yield can be rationalized, at least in part, by α, β -elimination of the chloride under the basic reaction conditions and to smaller extent, reaction of aryl-magnesium, a hard nucleophile with the ester based protections of C-3 and C-5 hydroxy groups in **40**.



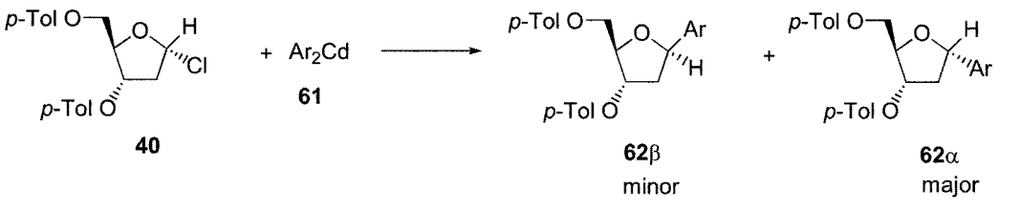
(i) Mg/THF, 40°C, then **40**, at r.t, overnight, 23% (R=F), 22% (R=CH_3);
(ii) NaOMe/MeOH 92% (R=F); 100% (R=CH_3)

Scheme 11

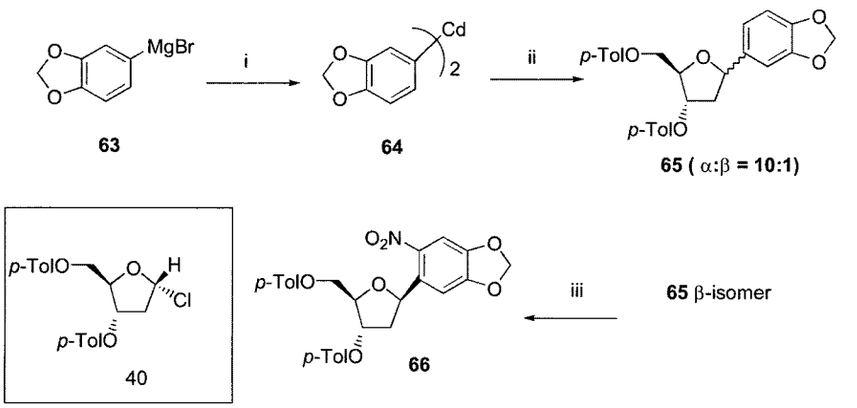
In an attempt to develop improved methods for the synthesis 2′-deoxy-*C*-aryl-nucleosides, Kool's group[26a] did a systematic study by the way of variation in the nature of the organometallic reagents. After experimentation with several metallophenyl species, such as PhLi, PhMgBr, Ph_2Cd, Ph_2Zn and Ph_2Hg in an ethereal solvent such as THF, it was concluded that use of diarylcadmium or diarylzinc reagents allows for an efficient synthesis of 2′-deoxy-*C*-aryl-nucleosides. These two organometallics are compatible with the base labile ester functionality in the chlorosugar **40**. Subsequent X-ray crystallographic and ^1H NOE studies showed that the primary products derived from these reactions were α-configured isomers, and not the desired β-isomers, which appeared only as minor products [26b] (**Scheme 12**). However, later on it was found that it is possible to equilibrate the major and also the undesired α-*C*-nucleosides to the desired β-anomers under acidic conditions in the presence of small amount of water.[27a] This observation definitely has increased the synthetic utility of Kool's protocol for 2′-deoxy-*C*-aryl-nucleosides by many folds. Recently the findings of Stivers *et al.* that trifluoroacetic (TFA) acid in dichoromethane[27b] and a combination of TFA and benzenesulfonic acid in dichoromethane[27c] serves as an effective catalyst for the desired anomeric epimerization in 2′-deoxy-*C*-aryl-nucleosides carrying electron-donating and electron withdrawing substituents respectively, has further strengthen the utility of the approach.

Recently using Kool's protocol, a novel photo-cleavable DNA base analogue, 2-deoxy-*C*-(nitropiperonyl)nucleoside **66** has been synthesized.[28] It involved reaction of ditoluoylribosyl chloride **40** with diarylcadmium reagent **64** derived from bezodioxol-4-yl Grignard reagent **63**. Reaction at room temperature in THF, resulted in high yields of 87% and α/β ratio as 10/1. Using Kool's *p*-TsOH/toluene equilibration procedure, α/β ratio of 10/1 was changed to 1/1.55, in favour of the desired β-isomer. Nitration of the β-isomer afforded the target 2-deoxy-*C*-(nitropiperonyl)nucleoside **66** (**Scheme 13**).

Incidentally the chloro-sugar **40** has been extremely useful for yet another derivative of considerable significance to arrive at 2-deoxy-*C*-furanoside frame work. The cyano derivative **67**α, β easily accessible[29] from the chloro-derivative and wherein the requisite C-C bond at the anomeric position is already established, has been extensively used towards this end. Three reagents commonly used to effect the conversion of **40** to **67**α, β are NaCN/DME,[29a] Et_2AlCN/Toluene,[29b] TMSiCN/$BF_3.OEt_2$[29c] The β/α anomers of the cyano derivative are easily separable using silica-gel chromatography (**Scheme 14**). The cyano functionality has been extremely handy at several occasions for the assembly of heteroaryl unit, de novo on the sugar



Scheme 12



(i) $CdCl_2$ (0.5 equiv), THF; (ii) **40** (0.76 equiv), rt, 6h, 87%; (iii) $Cu(NO_3)_2.3H_2O$, Ac_2O, rt, 0.5h, 90%

Scheme 13

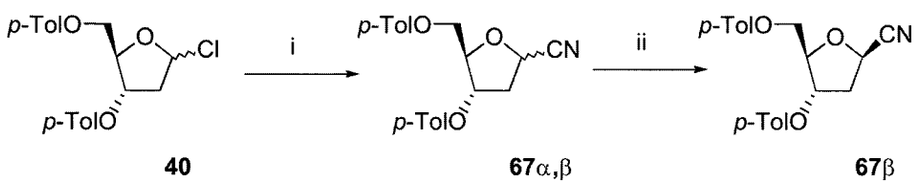
moiety.[30] Representative examples from the recent literature are delineated in **Scheme 15**.[29c]

The other two cyano derivatives of 2-deoxy-*D* -ribose (**Figure 5**), although less used, but with significant promise are **72**[31, 32, 33a] and **73**.[33b] Cyano derivative **72** in particular has paved the way for novel disubstituted pyrimidinyl-2-deoxy-*C*-nucleosides **78**. The cyano functionality in **72** offered an excellent handle to arrive at α, β-unsaturated acetylenic ketones through the intermediacy of Weinreb amide **75**. Hetero-annulation on these reactive acetylenic ketones **77** furnished the pyrimidinyl-2-deoxy-*C*-nucleoside analogues (**Scheme 16**).

Another elegant use of **72** towards the synthesis of 2-deoxy-*C*-heteroaryl-nucleosides has been reported by Seitz et al.[34] The imidoester **79**, obtained from the cyano compound **72**, undergoes inverse electron demand Diels-Alder reaction with tetrazine **80** to furnish the triazine **81**. Subsequently a second inverse electron demand Diels-Alder reaction with electron rich dienophile **82**, affords the *bis*-trifluromethyl substituted pyridine nucleoside **83**. (**Scheme 17**)

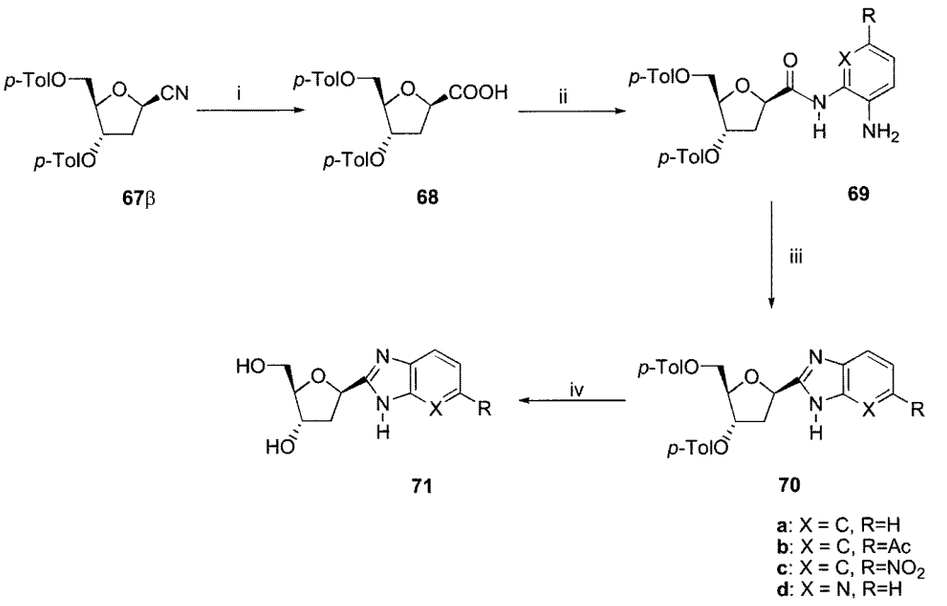
4.2 The Sugar, 2-deoxy-D-ribose as Electrophile in the Acyclic Form

The use of differently protected *acyclic* derivatives of 2-deoxy *D* -ribose (**Fig. 6**), has been documented rarely and this is probably due to their limited availability and lengthy synthetic procedures for preparing them. The derivative **41**, 2-deoxy-3,



(i) Several reagents and reaction conditions have been used: a) NaCN/DMF[29a]; b) Et_2AlCN in toluene[29b]; c) $TMSCN/BF_3.OEt_2$[29c]; (ii) α, β separation by silica gel chromatography.

Scheme 14



(i) aq.HCl, dioxane, 95%; (ii) DCC, coupling with *O*-diamine (75-92%);
(iii) AcOH, 40-50°C; (iv) NaOMe/MeOH, quantitative.

Scheme 15

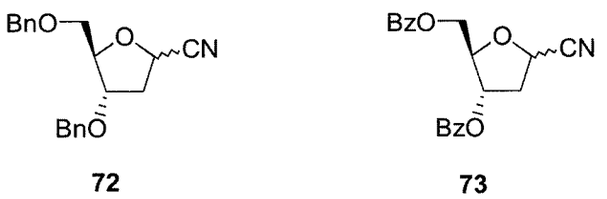
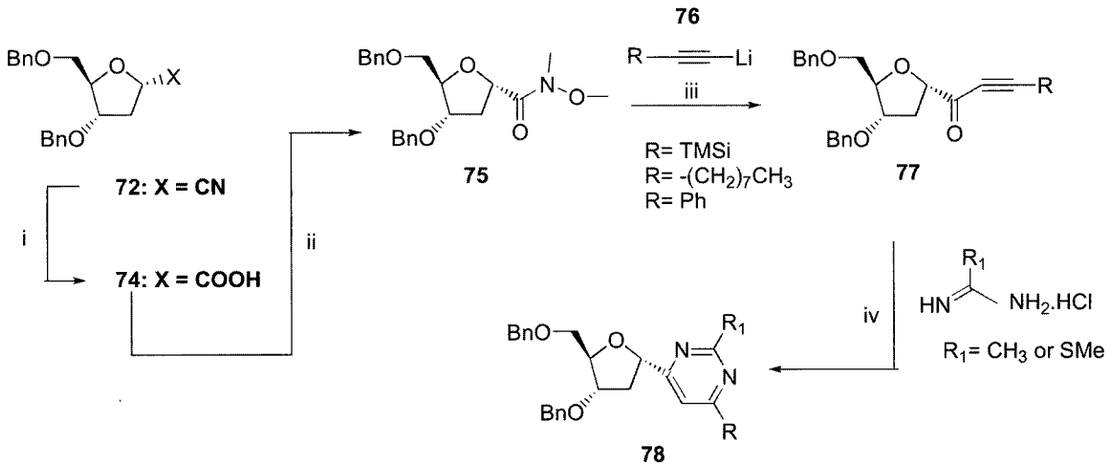


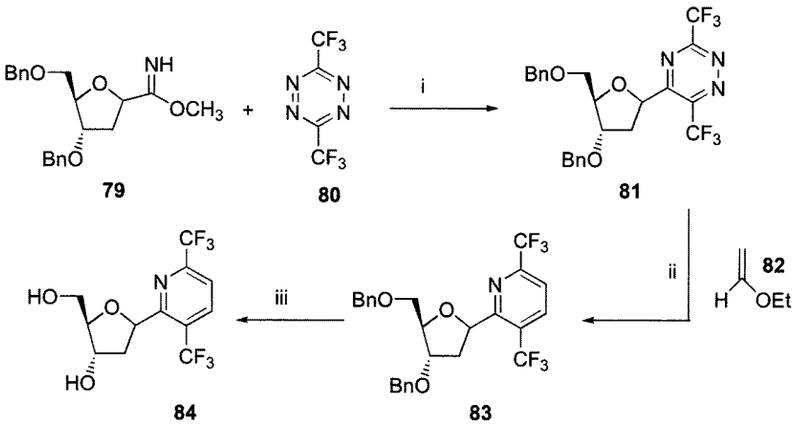
Fig. 5

4-bis-*O*-(4-methoxybenzyl)-5-*O*-(4, 4′–dimethoxytrityl)-*D* -ribose, was assembled for the first time by Eaton *et al.*[35] for the synthesis of pyridine based 2-deoxy-*C*-nucleosides. It required tedious seven step procedure starting from 2-deoxy *D* -ribose. In contrast, the derivative **43**, 5-*O*-[(*tert*-butyl)diphenylsilyl]-2-deoxy-3,4-*O*-isopropylidene-*aldehydo-D* -ribose was



(i) HCl, 1,4-dioxane,100 °C, 4h; (ii) α,α-dichloromethylmethyl ether, DCM, reflux, 5h, then Me(OMe)NH.HCl, NEt_3, DCM, rt, 24h; (iii) **76** (2 equiv), THF, -78 °C; 3h, then NH_4Cl (aq), -78°C to rt; (iv) Na_2CO_3, MeCN, H_2O, 80 °C, 24h.

Scheme 16



(i) Xylene reflux, 52%; (ii) Toluene reflux, 77%; (iii) DDQ, n-Hexane, 2d, reflux, 56%.

Scheme 17

conveniently prepared in four steps starting from the same material.[36] However, the derivative **42** was synthesized using isopropylidene protected *R*-glyceraldehyde as the starting substrate.[37] The carbon chain extension and the desired stereochemistry at C-3 carbon in **42** were achieved by Felkin-Anh addition of an allylzinc reagent to the aldehyde group.

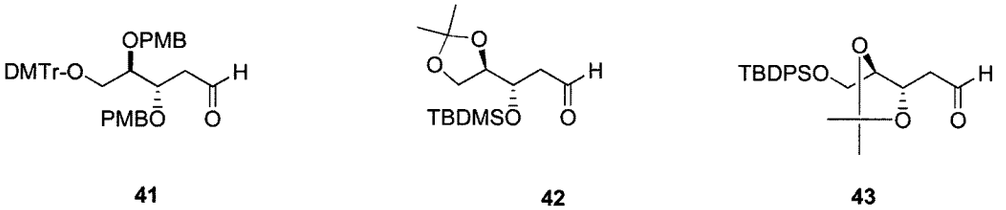


Fig. 6

Schultz and Romesberg demonstrated the usefulness of **41** and **42** in particular,[38] when difficulties were encountered in synthesizing naphthalene based nucleoside analogues **87** and **89** by the condensation of corresponding naphthylmagnesium halides **85** and **88** with the chloro derivative **40** (**Scheme 18**).

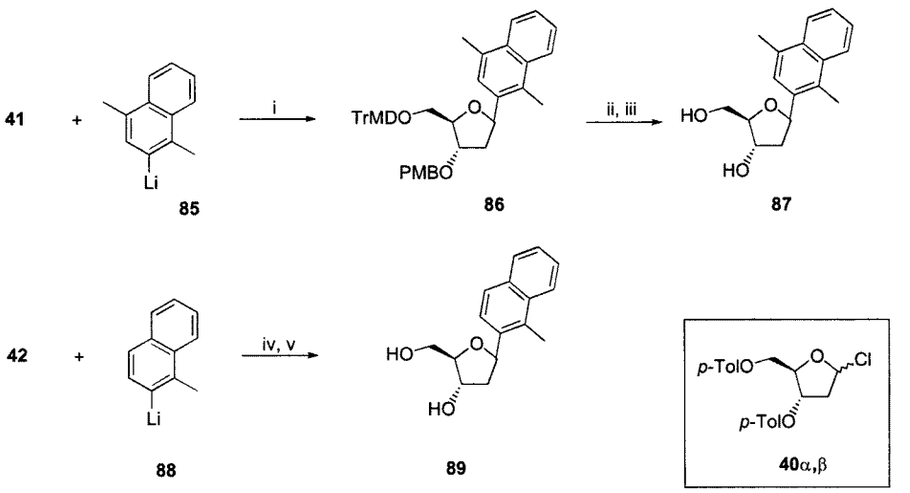
Naphthyllithium **85** and **88** smoothly reacted with the 2-deoxy-*D* -ribose derivative **41** and **42** respectively. Subsequent cyclisation and deprotection furnished the nucleoside derivatives **87** and **89** respectively.

Recently, another differentially protected derivative of 2-deoxy-*D* -ribose in the acyclic form, **43** has been used (**Scheme 19**). The protected Benzimidazole **90** and thiazolyl-benzimidazlole **91** were lithiated by LDA at -50 °C to furnish the corresponding 2-lithio derivatives **90a** and **91a** in quantitative yields.

These two lithiated heterocycles reacted with **43** to afford the corresponding pentitol derivative **92** and **93** in 60% yield and as a mixture of R/S diastereoisomers in the ratio of 7:3 respectively. Seperation of the distereoisomers in each case and mesylation of the *S*-isomer, followed by de-isopropylidenation led to the desired 2-deoxy-*C*-heteroaryl-nucleosides.

*4.3 The Sugar, 2-deoxy-***D***-ribose as Electrophile in the Higher Oxidation as Lactone*

Realizing that the key synthetic issue in any strategy would be the control of the stereochemistry at the anomeric center, Woski *et. al.* explored the use of protected 2-deoxyribonolactone **44** in lieu of α-chlorosugar **40** as the electrophilic sugar component for reaction with phenyllithium as a representative aryllithium.[39a] The other reason that prompted this study was the limited shelf-life (~2 weeks) of the α-chlorosugar **40**. However it would be appropriate to mention here that recently[40] the reasons for the limited shelf-life have been unfolded

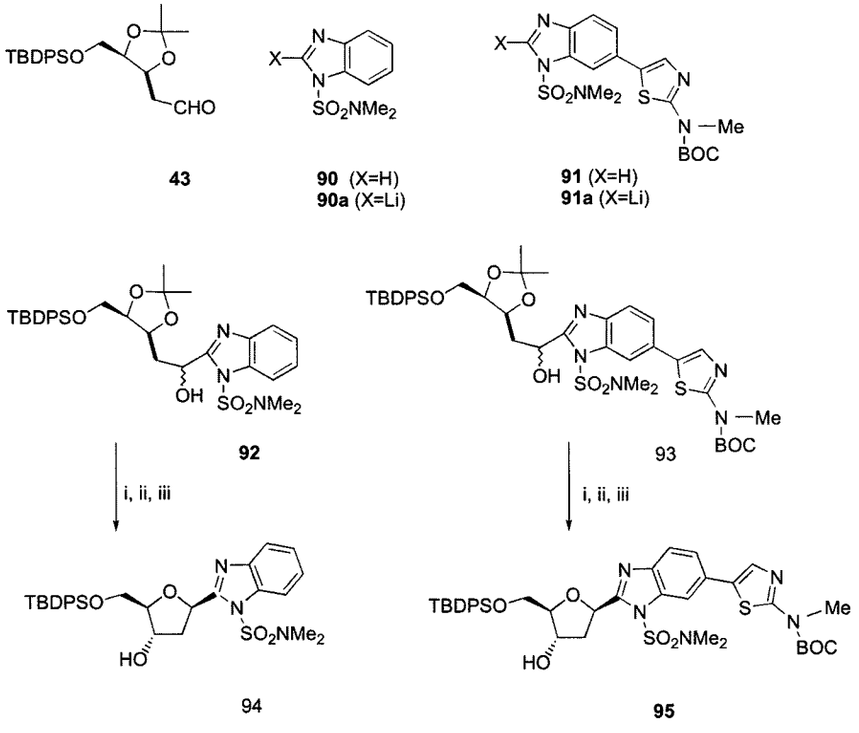


(i) MsCl, NEt_3, pyridine, 0 °C; (ii) AcOH; (iii) DDQ; (iv) MsCl, 0 °C; (v) TFA

Scheme 18

and suitable changes in the original procedure have resulted in the formation of the α-chlorosugar **40** as an indefinitely stable solid.

The lactone **44** used by Woski is α shelf-stable solid and is conveniently obtained in high yields by oxidation of the commercially available 2-deoxy-*D* -ribose **22** using aqueous bromine and subsequent treatment of the crude product with *tert*-butyldimethylsilyl chloride (TBDMS-Cl)/ imidazole. Interestingly, among the organometallics, phenyllithium, phenylmagnesium bromide and phenylcerium dichloride, only phenyllithium

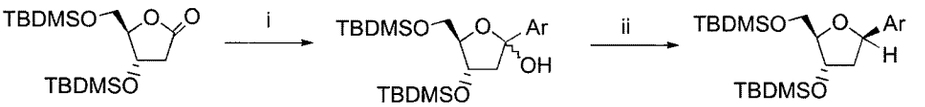


(i) Separation of the diastereoisomers using silica gel flash chromatography;
(ii) MsCl, Et_3N, DMAP, CH_2Cl_2, 88-90%; (iii) $SnCl_2.2H_2O$, CH_2Cl_2, 58-62%.

Scheme 19

successfully reacted with the lactone **44**. Although addition of phenyllithium at -78 °C and subsequent reductive deoxygenation using $Et_3SiH/BF_3.OEt_2$ led to the exclusive β-anomer, the yield of the two step model for 2′-deoxy-*C*-aryl-nucleosides was just moderate of 43% (**Scheme 20**).

The lactone **45** has been useful at two occasions for the synthesis of 2′-deoxy-*C*-aryl-nucleosides.[42,43] In a study aiming at DNA-like duplex without hydrogen bonded base pairs, Hunziker *et al.*[42] synthesized pentafluorophenyl-β-*D*-2-deoxyriboside **102** as shown in the **Scheme 22**.



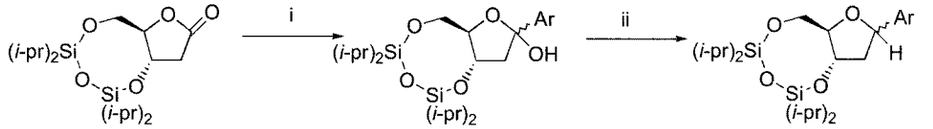
44 **96** **97**

a: Ar = phenyl
b: Ar = 2-tolyl
c: Ar = 3-tolyl
d: Ar = 4-tolyl
e: Ar =1-naphthyl

(i) ArLi, -78 °C, THF, aq. work-up; (ii) Et_3SiH, $BF_3.OEt_2$, CH_2Cl_2, -78 °C

Scheme 20

Also further systematic studies by Woski *et al.*[39b] with the view to improve the efficiency revealed unexpected surprises. The addition of aryllithium to the lactone was very sensitive to substitution on the aryllithium reagent. For example, reactions of **44** with 4-tolylithium, 3-tolylithium or 2-naphthyllithium followed by reductive deoxygenation with $Et_3SiH/BF_3.OEt_2$ produced significantly diminished yields of the corresponding 2′-deoxy-*C*-aryl-nucleosides (10, 8 and 16% respectively). Aryllithiums with substitutions adjacent to the carbanion (2-tolylithium and 1-naphthyllithium) produced none of the desired products. The bulky TBDMS protecting groups probably offered to steric hinderence to the approach of the aryllithium as the possible cause of the poor reactivity, it necessitated the search for an alternative protection. The bifunctional dioxolane protecting group introduced by Markiewicz,[41] prompted to the lactone **45** as a possible alternative with diminished steric influence. In fact restriction of the motion by way of imposing cyclic structure proved successful. The lactone **45** was prepared in the same way as **44** and by replacing *tert*-butyldimethylsilyl chloride/imidazole with 1, 3-dichloro-1,1,3,3-tetraiso-propyl di-siloxane/imidazole for the simultaneous protection of the hydroxyl groups at C-3 and C-5. Although the alternative lactone **45** proved less sensitive to the nature of aryllithium (**Scheme 21**),[39b] the isolated yield of the disiloxane protected 2′-deoxy-*C*-aryl- nucleosides **99** after the two-step protocol continued to remain low (17-56%), but still with high stereoselectivity in favour of the desired β-anomer.

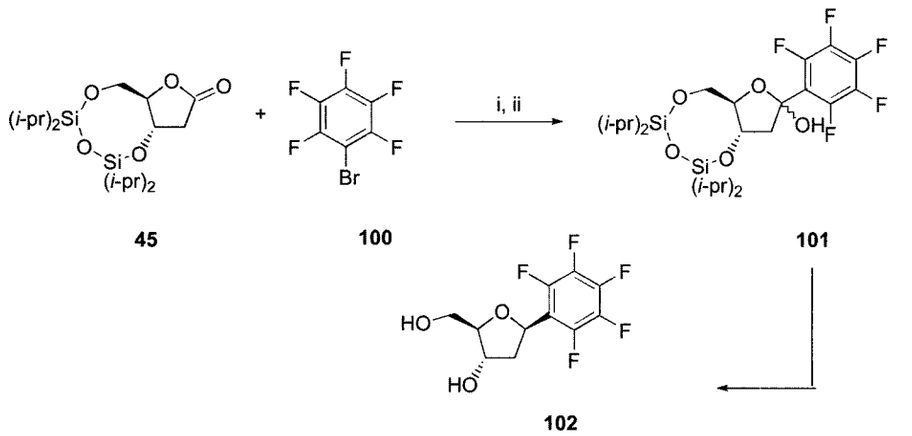


45 **98** α,β **99** α,β

(i) ArLi, -78 °C, THF; (ii) Et_3SiH, $BF_3.OEt_2$, CH_2Cl_2, -78 °C.

a: Ar = phenyl, 56%, β : α = 11:1
b: Ar = 4-methyl phenyl, 24%,β : α = 28:1
c: Ar = 3-methyl phenyl, 35%, β : α = 15:1
d: Ar = 2-methyl phenyl, 17%, β : α = 6.5:1
e: Ar = 3,5-dimethyl phenyl, 34%,β : α = 11:1
f: Ar = 1-naphthyl, 34%,β : α = 11:1
g: Ar = 2-naphthyl, 38%,β : α = 10:1

Scheme 21



(i) **100** (2.0 equiv), BuLi (1.8 equiv), Et_2O, -78 °C, 1h, then **45** (1.0 equiv), -78°C, 1h. (ii) Et_3SiH, $BF_3.OEt_2$, CH_2Cl_2, -78 °C, Bu_4NF, THF, rt.

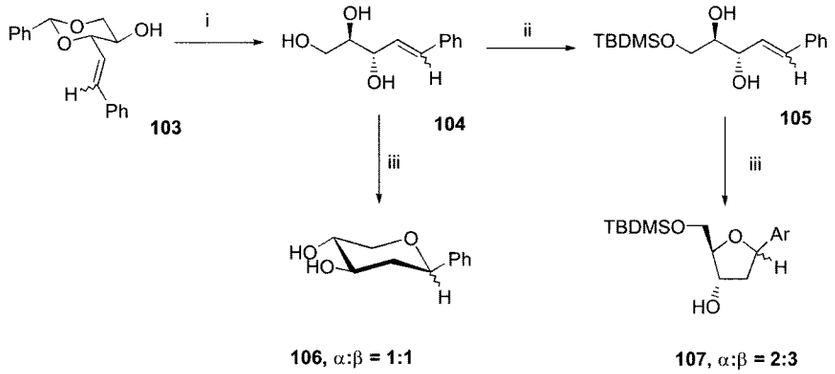
Scheme 22

5 Other Less Used and New Approaches of Significant Importance and Potential

Conceptually Wittig Olefination on benzylidene protected *D*-erythrose should afford the framework **103** for exploring intramolecular cyclisation to arrive at 2-deoxy-*C*-phenyl ribofuranoside. Polt *et al*[44] have used a multi-step scheme to arrive at **103** and studied the mercuric ion initiated cyclisation towards this concept. The results obtained were not very promising. Several attempts to affect cyclization in **103** gave no trace of the desired *C*-nucleoside. The triol **104** thus obtained after hydrolysis of **103** underwent cyclisation to afford 1:1 mixture of the α/β phenyl-*C*-glucoside in the *pyranose* form. The protection of the primary hydroxyl in **104** and subsequent cyclization furnished the desired target **107 (Scheme 23)**.

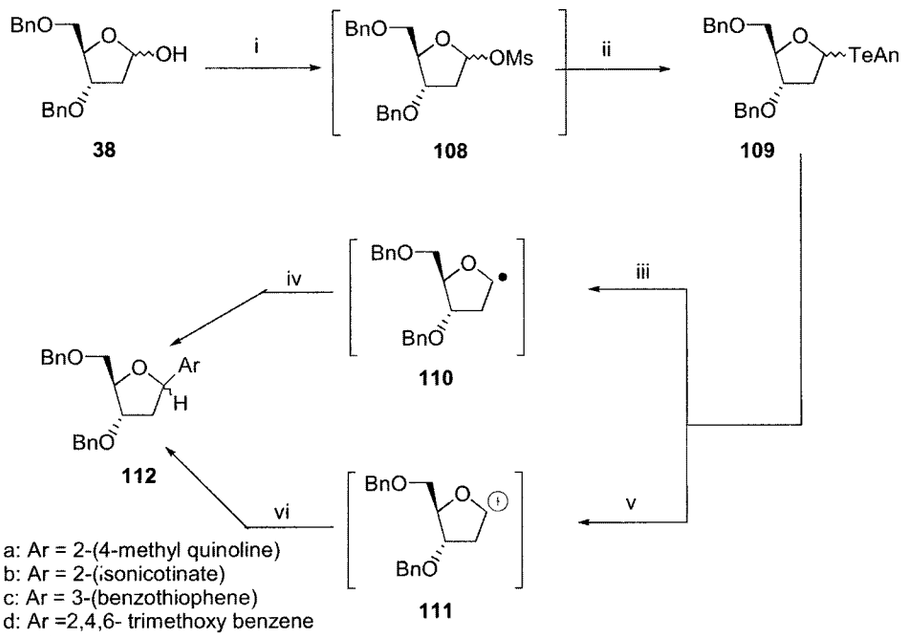
Based on the information that tellurides have exceptional radicophilicity, electrophilicity and nucleophilicity, Yokoyama *et al* [45] synthesized 2-deoxy-*D* -ribofuranosyltelluride **109** and investigated its use towards the synthetic target of 2-deoxy-*C*-aryl or hetero-aryl nucleosides. Under the influence of triethylborane as radical initiator, **109** afforded the corresponding anomeric radical **110,** which coupled with electron deficient heteroaromatics to furnish **112a** and **112b**. The same ribofuranosyl telluride **109** under the influence of Lewis acid such as $BF_3.OEt_2$ produced the anomeric cation **111** for coupling with electron rich aromatics. These conditions paved the way for the synthesis of **112c** and **112d (Scheme 24)**.

Calter *et al*[46] have used rhodium carbenoid insertion between O-H bond in the aldol frame-



(i) H_3O^+; (ii) TBDMSCl/imidazole; (iii) $Hg(OAc)_2$, $NaBH_4$, 66%.

Scheme 23

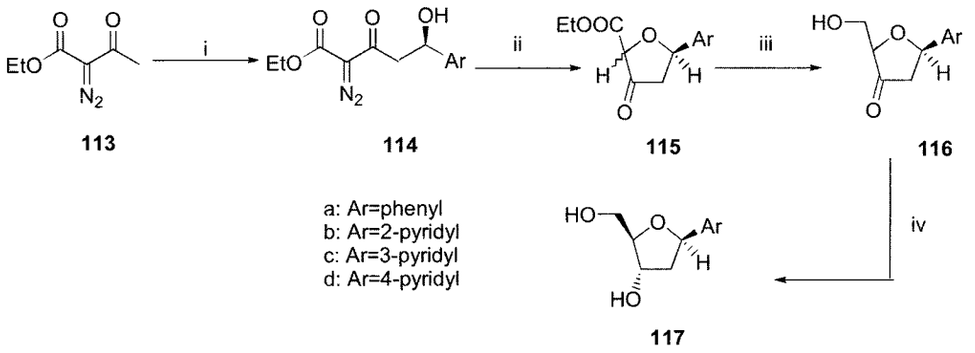


(i) MsCl, Et_3N, THF, 50 °C; (ii) $(AnTe)_2$, $NaBH_4$, THF/EtOH; (iii) Et_3B, $CHCl_3$; (iv) 4-methyl isoquinolinium triflate for **112a**, methyl isonicotinate triflate for **112b**; (v) BF_3OEt_2, $CHCl_3$; (vi) benzothiophene for **112c**, 1,3,5-trimethoxybenzene for **112d**.

Scheme 24

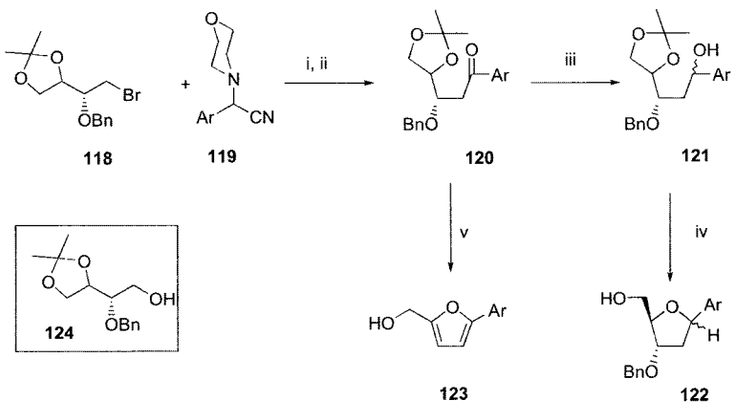
work to construct the tetrahydrofuran ring of the 2-deoxy-*C*-aryl-nucleosides. The strategy, therefore, constitutes a de novo synthesis of a sugar unit. The scheme started with readily available diazo compound **113**. In the first step an aldol reaction incorporated the aryl residue to arrive at **114**. This was followed by a key rhodium catalyzed O-H insertion leading to the construction of the sugar ring. Functional group transformation led to the target molecule **117** (**Scheme 25**).

In our own group we have been successful in developing a yet another simple and versatile approach.[47] It involves the coupling of a differentially protected *erythro* configured bromo-derivative **118** with arylaminonitriles **119** as the acyl-anion equivalent (**Scheme 26**). The ready availability of



(i) TMSOTf, Et_3N, CH_2Cl_2, ArCHO, $BF_3.OEt_2$; (ii) 1 mol% $Rh_2(OAc)_4$, benzene; (iii) a) TBSCl, Et_3N, CH_2Cl_2, r.t; b) DIBAL, THF, -78°C; c) $Et_3N.HF$, CH_2Cl_2, 0°C; (iv) $NaB(OAc)_3H$,AcCN, r.t.

Scheme 25



(i) **119** (1.1 equiv), NaH in DMF, followed by **118** (1equiv), (ii) $CuSO_4.5H_2O$, MeOH,H_2O, 70-75% (over two steps); (iii) $NaBH_4$, CH_3OH, 0 °C quantative; (iv) p-TSA,THF, 60-65%; (v) Trace of H^+in $CDCl_3$ or 1% I_2 in methanol, 72%

Scheme 26

a plethora of aryl-acyl anion equivalents in the literature[48] and its elegant use towards *C*-furanoside[49a,b] and pyranoside skeleton,[49c] coupled with recently disclosed convenient access to enantiopure erythritol derivative **124**,[50] justifies the simplicity and versatility of the new strategy. Our systematic investigation revealed that the sequence, reduction of the carbonyl group followed by acid catalyzed cyclization on the arylketones **120** is crucial for the success.[51] The reverse sequence fails and any attempt of acid catalyzed cyclization of the aryl-ketones **120**, with the hope of subsequent deoxygenation and arriving at **122,** only leads to a furan derivative **123**.

6 Conclusion

The information that changing the structure of the base moiety attached to 2-deoxyribose through useful strategies for probing structural and functional aspects of DNA has attracted synthetic organic chemists to play a prominent role from the synthetic aspect. The attachment of the modified nucleobase to the 2-deoxysugar unit through C-C bond in particular and the associated promise of enhanced stability have made 2-deoxy-*C*-heteroaryl-nucleosides very ambitious targets for synthetic endeavors. Some of these modified nucleosides have been excellent reporter groups for physical and biochemical studies of structure and function. Fluorescent tagged DNA bases in particular, allow for placement and probing even near the middle of a stretch of DNA. Studies from the Kool's group[52] aiming at a new class of DNA base analogues to serve as biophysical probes have been proved to be very significant.

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