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The evolution of comprehensive strategies for furanoid glycal synthesis and their applications†

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Cyclic enol ether frameworks, especially stereochemically pure furanoid and pyranoid glycals are well known highly functionalized chiral building blocks. Furanoid glycals have been shown to possess great potential, as they have been used as key intermediates for the synthesis of structurally diverse molecules

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including natural products with various biological activities since their discovery in 1963 by Ness and Fletcher. In this review on furanoid glycals, efforts are made to exhaustively compile the work centered on synthesis and utility of furanoid glycals since the inception to date. This review aims to highlight the importance of furanoid glycals and the strategies developed over the years for their synthesis. Attention has also been focused on the use of these furanoid glycals toward the synthesis of natural and unnatural products including *C*-and *N*-nucleosides of biological importance. Apart from that, efforts are also devoted to cover the significant applications of these furanoid glycals for stereoselective synthesis of various cyclic and acyclic key intermediates of significant interest.

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1. Introduction

Carbohydrates represent one of the most privileged classes of naturally occurring versatile building blocks in synthetic organic chemistry due to their wealth of unique functional, conformational, and stereochemical information. The diversity and availability of these relatively cheap chiral compounds has led to their use as starting materials for the design and syntheses of naturally occurring compounds and biologically important molecules.[1] The preparation of attractive building blocks from carbohydrates and their use for the synthesis of various biologically active simple or complex natural products has received considerable attention from organic chemists. Therefore, the stereocontrolled synthesis of chiral building blocks (CBBs) is an important objective in organic chemistry. Over the last several years our group has been working toward the synthesis of enantiomerically pure sugar derived building blocks and their utilization to accomplish the total synthesis of target biologically relevant natural products[2b,d,g,h] and natural product like molecules.[2a,c,e,f,i] Recently our research group has reviewed glycal derived δ-hydroxy α,β-unsaturated aldehydes (Perlin aldehydes).[3a]

While there are many carbohydrate derivatives, monosaccharides occupy a significant place among them as starting materials. Glycals, prepared from hexoses and pentoses, are most important and well known highly functionalized CBBs and find their huge applications in 'chiron' approach synthesis.[3b,c] They are highly reactive due to their enol ether geometry (a double bond between the carbon atoms 1 and 2 of the ring). There are two kinds of glycals: (i) pyranoid glycal **I** (derived from hexose), (ii) furanoid glycal **II** (derived from pentose) (Fig. 1).

A considerable effort has been dedicated toward the synthesis of pyranoid glycals and furanoid glycals. In recent years, interest has been devoted to synthesis of furanoid glycals, owing to the fact that they have been used as key intermediates in syntheses of structurally diverse compounds with various biological activities such as polyether antibiotics,[4] 6-*epi*-leukotrienes C & D,[5] palladium-mediated coupling reaction leading to *C*-nucleosides,[6] antiviral and antitumour *C*-nucleosides,[7] α-arabino nucleosides,[8] 2′,3′-dideoxynucleosides[9] and more recently 2′-deoxynuleosides.[10]

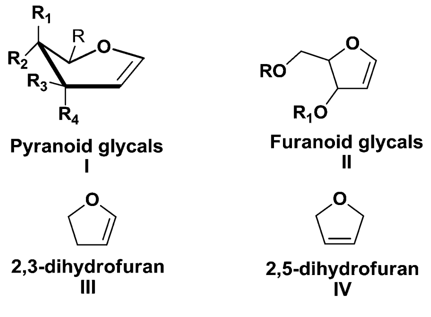

Fig. 1 General structures of pyranoid glycals (I), furanoid glycals (II), 2,3-dihydrofuran (III) and 2,5-dihydrofuran (IV).

There are a large number of reports on the synthesis and uses of furanoid glycals. The versatile application of furanoid glycals inspired us to compile the wholesome work centered around their synthesis and applications since the inception to date in the form of a review. This review mainly focuses on various synthetic routes for the preparation of furanoid glycals and their applications toward synthesis of important 'chiral building blocks', various kinds of natural and unnatural products of biological importance and *C*- & *N*-nucleosides. We have tried to include many recent examples in this review that covers our studies till date, and any omissions on this wide topic are unintentional. It should be noted that, only synthesis and applications of furanoid glycals are described here. Other reactions, in which 2,3- and 2,5-dihydrofurans (**III**, **IV**) involve are not described here (Fig. 1).

2. Literature reports on synthesis of furanoid glycals (FGs)

Glycals (pyranoid and furanoid glycals) are important intermediates in the synthesis of a variety of carbohydrate derivative. In 1913, Fischer and Zach[11] first synthesized 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol. Inspired by the reactivities of glycals and to report the first synthesis of furanoid glycal (FG), Ness and Fletcher tried to synthesise furanoid glycal from tri-*O*-benzoyl-α-D-arabinofuranosyl bromide after several modification of Fisher and Zach's method.[12] But they failed to achieve their goal.

However, they successfully synthesised 1,4-anhydro-3,5-di-*O*-benzoyl-2-deoxy-D-*erythro*-pent-1-enitol **4** in 1963, known to be the first glycal derivative with a furanose structure, starting from 3,5-di-*O*-benzoyl-2-*O*-*p*-nitrophenylsulfonyl-β-D-ribosyl bromide **3**, which was easily prepared from 1,3,5-tri-*O*-benzoyl-α-D-ribose **1** in two steps.[13] The free hydroxyl group in **1** was nosylated with NsCl in the presence of pyridine to obtain nosyl derivative **2**. It was brominated at C-1 with HBr in AcOH to afford 3,5-di-*O*-benzoyl-2-*O*-*p*-nitrophenylsulfonyl-β-D-ribosyl bromide **3**, which was ultimately treated with NaI in acetone solution at a low temperature to obtain crystalline FG **4** in 72% yield (Scheme 1). While its reaction in DCM with MeOH at room temperature gave the dihydro furan **5**, the fufuryl benzoate **6** was obtained when **4** in acetone was allowed to react with water.

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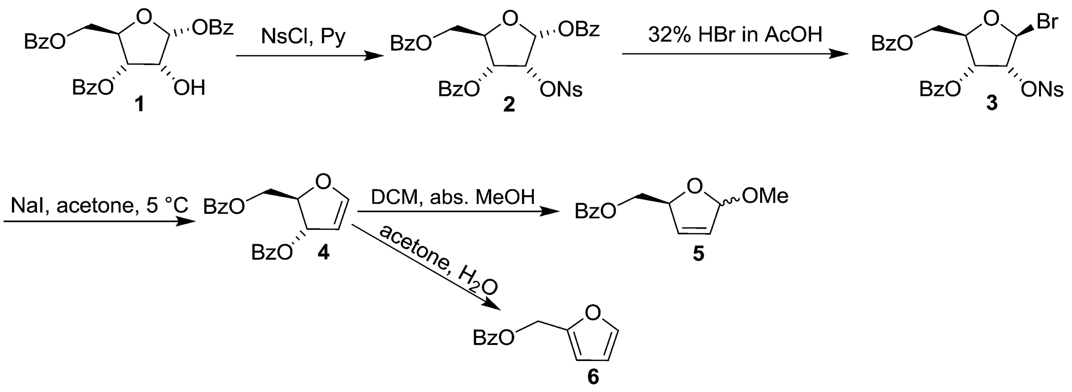
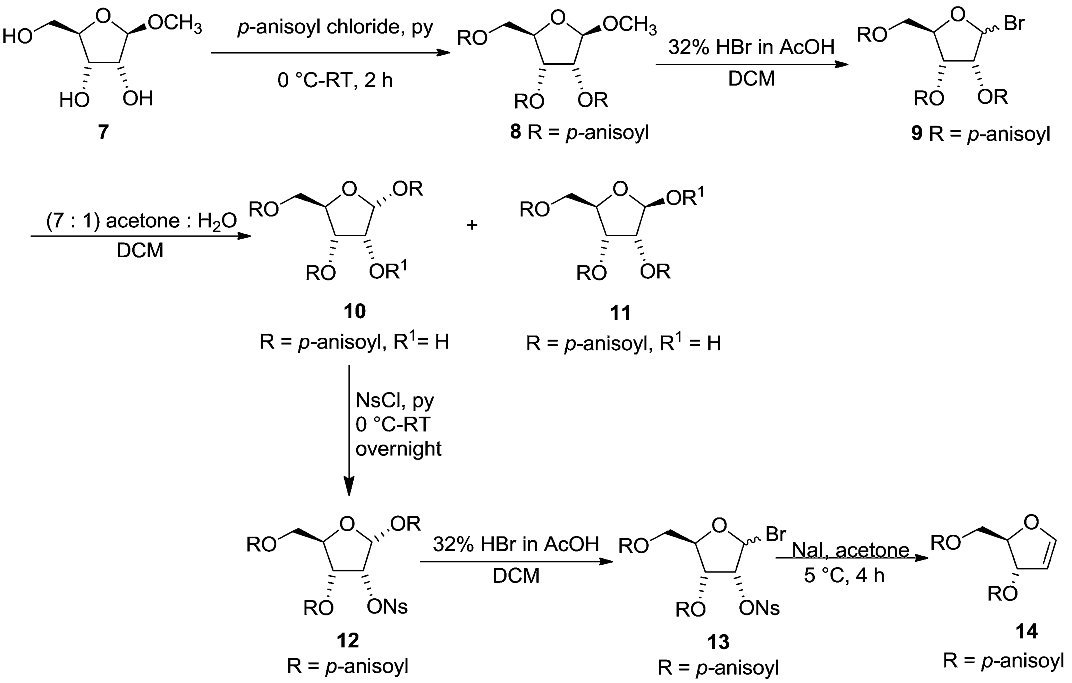


Scheme 1

After the synthesis of labile furanoid glycal **4**, Ness *et al.* synthesised 3,5-di-*O*-*p*-anisoyl-1,2-dideoxy-D-*erythro*-pentofuranos-1-ene **14** and showed that greater the nucleophilicity of the substituent at C-3 of furanoid glycal **14**, the lesser would be the tendency to form aromatic products. Its synthesis was started from methyl-β-D-ribofuranoside **7**. It was first acylated with *p*-anisoyl chloride to obtain **8** followed by its bromination with 32% HBr in AcOH to give bromoderivative **9**. Its hydrolysis and subsequently crystallization of the resulting product mixture with acetone and water (7 : 1) in DCM yielded isomeric hemiacetals 1,3,5-tri-*O*-*p*-anisoyl-α-D-ribofuranose **10** and 2,3,5-tri-*O*-*p*-anisoyl-β-D-ribofuranose **11**. Compound **10** was nosylated with *p*-nitrophenyl sulphonyl chloride (NsCl) in pyridine at 0 °C to give **12** in good yield. It was brominated with 32% HBr in acetic acid to furnish **13**, which was treated with NaI in acetone solution at 5 °C to obtain crystalline furanoid glycal **14** in 67% yield (Scheme 2).[14]

Bischofberger and Hall attempted to prepare the stable FGs[15] by the modification of Fischer and Zach's method in the year 1976.[13] However, their method failed to deliver the desired glycals due to the tendency of C-3 substituent to undergo allylic rearrangement. To get rid of this problem, a series of differently substituted furanose derivatives (**15a–d**) were prepared, where C-3 substituents were less susceptible to allylic rearrangement.[15a,b] Having these precursors in their hand, they prepared FGs (**19a–d**) by modifying Fischer and Zach's method for the preparation of glycals (Scheme 3, Table 1).[15c] The modified method involved the highly reactive cationic species (**17a–d**), which can either accept two electrons and lose an acetoxyl anion to form the glycals (**19a–d**), or can combine with hydroxyl or acetoxyl anions to give the free aldoses (**18a–d**) or starting materials (**15a–d**). The glycals **19a** and **19b** were obtained in moderate yields whereas **19c** and **19d** in low yields. All of them were stable on silica gel and stored under N_2 at −5 °C for 6 months. Compounds **20a** and **5** were



Scheme 2

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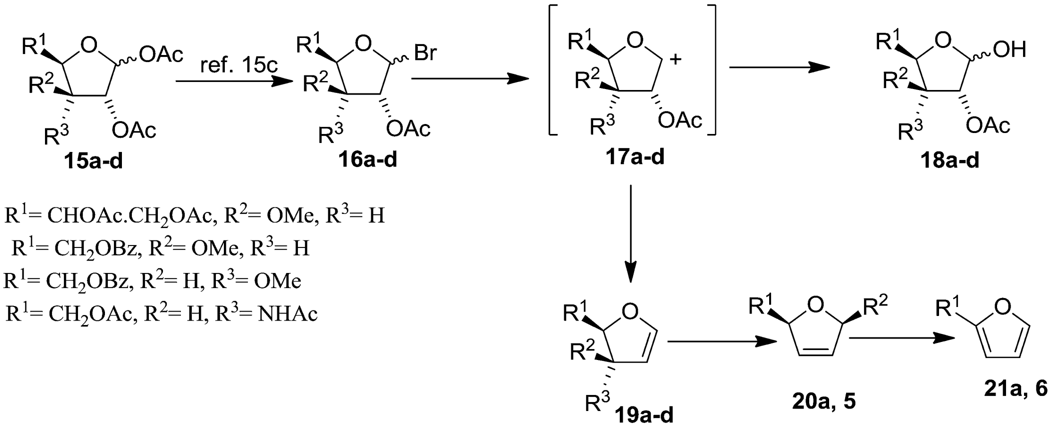


a R^1= CHOAc.CH_2OAc, R^2= OMe, R^3= H
b R^1= CH_2OBz, R^2= OMe, R^3= H
c R^1= CH_2OBz, R^2= H, R^3= OMe
d R^1= CH_2OAc, R^2= H, R^3= NHAc

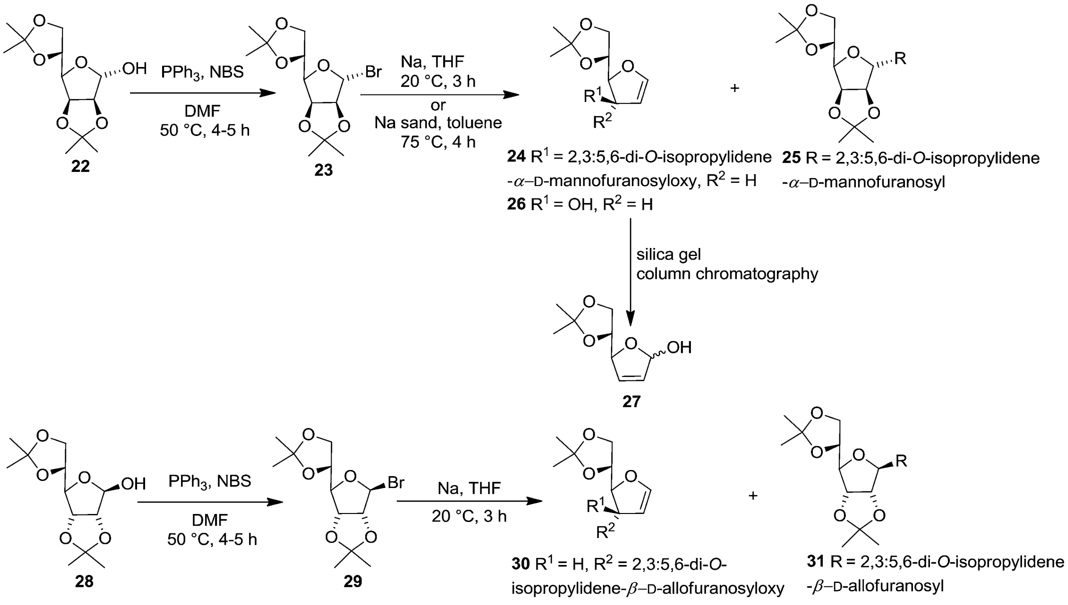
Scheme 3

Table 1 Product yields of furanoid glycals (**19a–d**) by modified Fischer and Zach's method from substituted furanose derivatives (**15a–d**)

	Yields of products (%)				
Starting material	Furan (**21a**, **6**)	Glycal (**19a–d**)	2,3-Unsaturated compound (**20a**, **5**)	Staring material (**15a–d**)	Hydroxyl compound (**18a–d**)
15a	1	26	2	3	51
15b	2	20	5	5	48
15c		6		5	83
15d		3		18	29

generated from their respective glycals **19a,b** by 1,3-sigmatropic shift of the methoxy groups, whereas the furans **21a** and **6** were produced by the decomposition of **19a** and **19b**, respectively (Scheme 3).[15d]

In 1977 Jordaan *et al.* reported an alternative method for the preparation of furanoid glycals by the reduction of suitably protected furanosyl bromides with sodium or potassium in aprotic solvents.[16a] 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **22** derived bromo derivative **23** (ref. 16*b*) on treatment with an excess of sodium in dry THF at 20 °C for 3 h gave furanoid glycal **24** in 59% yield and a trace of 1,1′-disaccharide **25** (2% yield). Treatment of the mannofuranosyl bromide **23** with



Scheme 4

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sodium sand in toluene at 75 °C for 4 h gave low yields of **24** (9%) as well as the 1,4-anhydrohex-1-enitol **26** (11%). The glycal **26** was unstable and rearranged during chromatography on silica gel to the isomeric compound **27** (Scheme 4).

In the similar way, reduction of 2,3:5,6-di-*O*-isopropylidene-β-D-allofuranosyl bromide **29**, derived from **28**,[16b] with sodium in THF (20 °C, 3 h) gave furanoid glycal **30** in 69% yield and 1,1′-disaccharide **31** (2% yield) (Scheme 4).

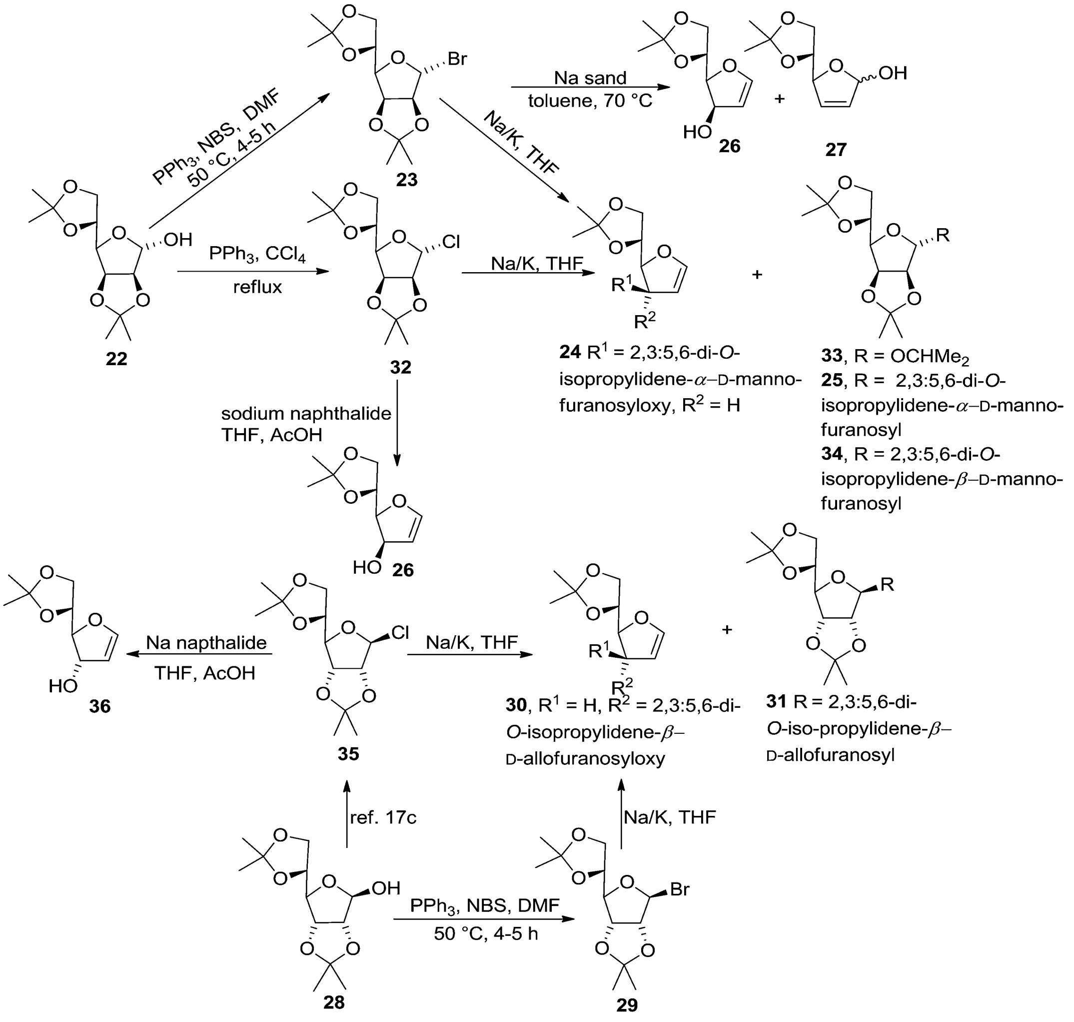
In 1978, the same group discussed an alternative route for the synthesis of furanoid and pyranoid glycals.[17a] While treating 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **22** derived furanosyl chloride **32** (ref. 17*b*) with sodium naphthalide in THF followed by acetic acid furnished **FG 26** in 59% yield, under the identical reaction condition furanosyl chloride **35** (derived from **28**) yielded FG **36** in 54% yield (Scheme 5).

On the other hand, treatment of furanosyl chloride **32** and furanosyl bromide **23** each with Na or K metal in THF instead of sodium naphthalide gave 3-*O*-furanosyl furanoid glycal **24** as the major product along with glycoside **33** and disaccharides **25**, **34** as by-products. Similarly, the furanosyl chloride **35** (ref. 17*c*) and the analogous bromide **29**, gave only the 3-*O*-furanosyl glycal **30** (69%) and a trace of the disaccharide **31** (Scheme 5).

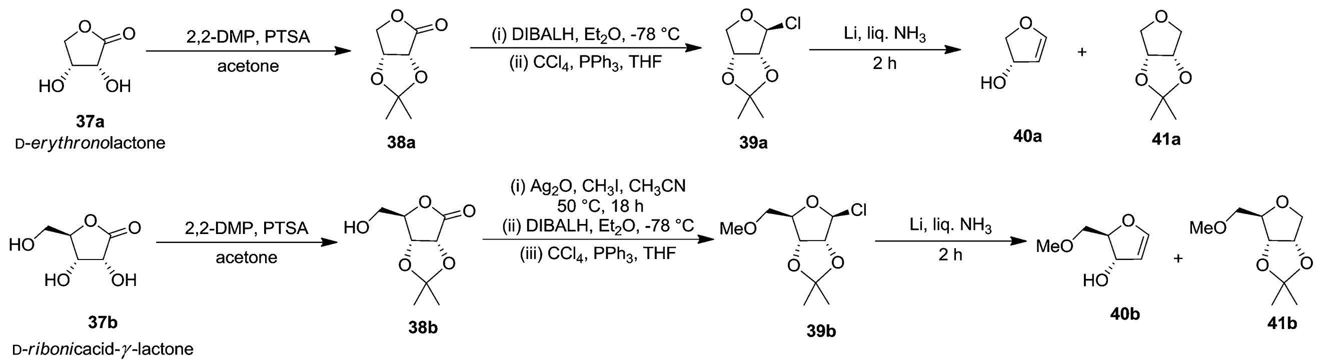
Further, warming furanosyl bromide **23** with sodium sand in toluene at 70 °C afforded the glycal **26** in low yield along with its isomeric 2,5-dihydro derivative **27** (Scheme 5).

In the same year, Ireland and co-workers developed a general procedure for the synthesis of high yielding 3-hydroxylated FGs, in 4 steps, starting from D-erythronolactone **37a** and from D-ribonic acid-γ-lactone **37b** in 5 steps, involving the reductive fragmentation of 2,3-*O*-isopropylidene protected furanosyl chloride with Li in liquid ammonia as a key step (Scheme 6).[4,18]

The starting material 2,3-*O*-isopropylidene-β-D-*erythro*-furanosyl chloride **39a** was prepared from D-erythronolactone **37a** in 79% overall yield by a sequence of reactions that involves acetonide formation of D-erythronolactone **37a** followed by partial reduction of the resulting acetonide **38a** with DIBALH in Et_2O at −78 °C to an intermediate 2,3-*O*-isopropylidene-D-erythrose, which was immediately treated with CCl_4 and Ph_3P in THF to obtain furanosyl chloride **39a**. Its reduction with 4 equiv. of Li in liquid NH_3 in the presence of 6 equiv. of NH_4Cl afforded a mixture containing glycal **40a** and THF **41a** in a ratio of 6 : 1 (NMR) with 60% yield. They also used D-ribonic-acid-γ-lactone **37b** as the starting material in their study to achieve the synthesis of furanoid glycal **40b**. The acetonide protection of the



Scheme 5



Scheme 6

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lactone was done by adopting the standard process to obtain acetonide **38b.** Methylation of its primary hydroxyl group with $Ag_2O/CH_3I/CH_3CN$ at 50 °C for 18 h, followed by reduction of the resulting *O*-methyl derivative with DIBALH in Et_2O at −78 °C for 1 h gave hemiacetal in 90% overall yield, which on treatment with $CCl_4/PPh_3/THF$ resulted furanosyl chloride **39b** in 90% yield. Its reduction with Li in liquid NH_3 as described above, afforded a mixture of glycal **40b** and the corresponding THF derivative **41b** in a ratio of 6 : 1 (NMR) with 75% yield. It was also reported there that the mixture was not separated by silica gel column chromatography because the furanoid glycal resulted poor recovery after purification (Scheme 6).

This group again utilized acetonide **38b** for the synthesis of furanoid glycal **45.**[4] The MOM protected lactone **42**, prepared from **38b** by treating with chloromethyl methyl ether (MOMCl) in the presence of diisopropylethylamine ($(^iPr)_2EtN$) in DCM, on reduction with DIBAL-H at −78 °C provided lactol **43.** Its chlorination with PPh_3 and CCl_4 in THF gave the chloride **44.** Its reduction with Li in liquid NH_3 at −78 °C yielded a mixture of glycal **45** and THF **46** in the ratio 6 : 1 with 93% overall yield (Scheme 7).

Under identical reaction condition furanosyl chlorides **32** yielded furanoid glycal **26** in 75% yield along with THF **47** in 9% yield (Scheme 7).

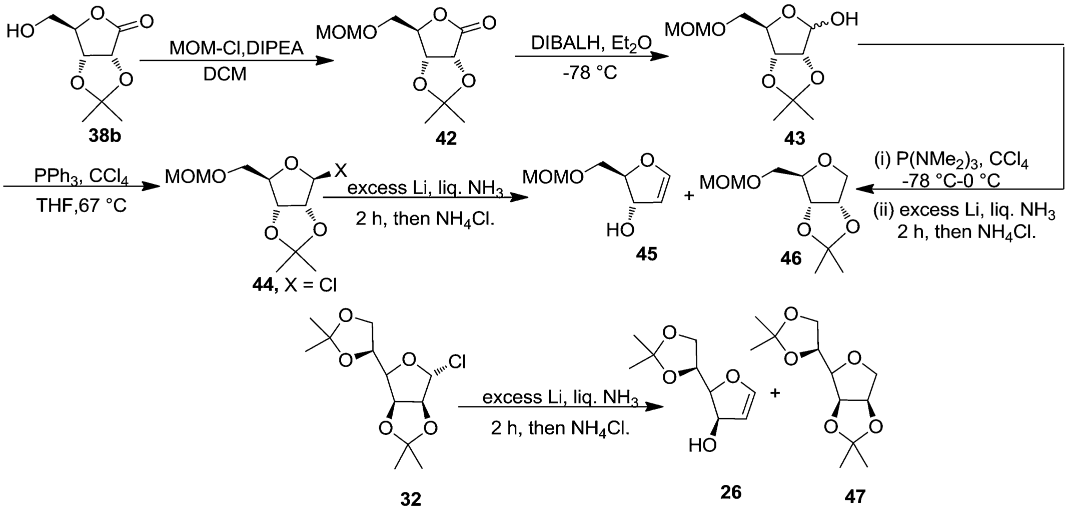
Due to the instability of the intermediate chlorides formed in this process, this group further examined an alternative method for the transformation of lactols to glycals. Hexamethylphosphorus triamide (tris-(dimethylamino)phosphine, TDAP) reacts at very low temperatures with CCl_4 in the presence of alcohols to form adducts of type **48** (Fig. 2).

First TDAP was added to a solution of lactol **43** and CCl_4 in THF at −78 °C. The resulting reaction mixture was warmed to 0 °C and then immediately it was added to a solution of excess Li in liquid NH_3 to afford a mixture of **45** and **46** in 6 : 1 with 93% yield after passing the crude product mixture through silica gel to remove HMPA (Scheme 7).

After that, they showed ester enolate Claisen rearrangement on furanoid glycal esters **48** and **50** derived from **45** and **26** respectively. These esters were prepared by the reaction of a lithium alcoholate with the appropriate butanoyl chloride and propanoyl chloride respectively, and the resulting solution of ester was used immediately for the Claisen rearrangement. Silyl

$$ROP^+(NMe_2)_3\ Cl^-$$

Fig. 2 Adduct **48**.



Scheme 7

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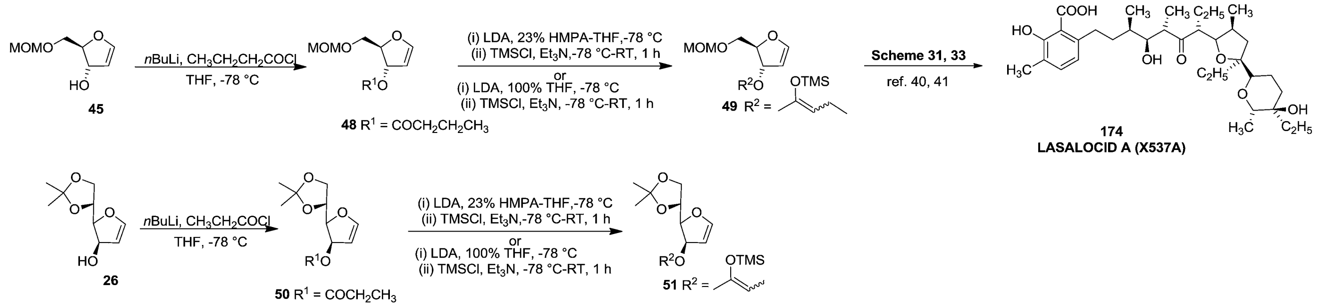
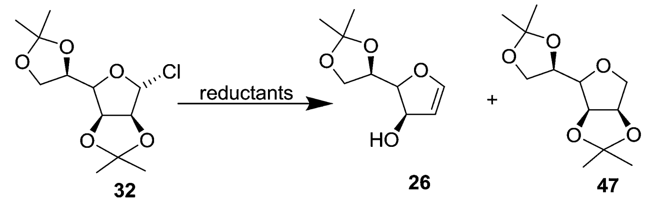


Scheme 8



Scheme 9

Table 2 Reductive fragmentation of the model furanosyl chloride **32** to obtain glycal **26**

Reductants	Yield of 26 (%)	26 : 47
Li/NH$_3$[a]	75%	7.9 : 1
Na/NH$_3$[a]	77%	10.7 : 1
K/NH$_3$[a]	79%	15.0 : 1
SmI$_2$[b]	0%	—
Sodium naphthalene[c]	82%	>50 : 1
Lithium benzophenone[d]	NR[h]	—
Sodium anthracene[e]	NR	—
Sodium trimesitylborane[f]	70%	>50 : 1
Lithium 4,4′-di-*tert*-butylbiphenyl[g]	94%	>50 : 1

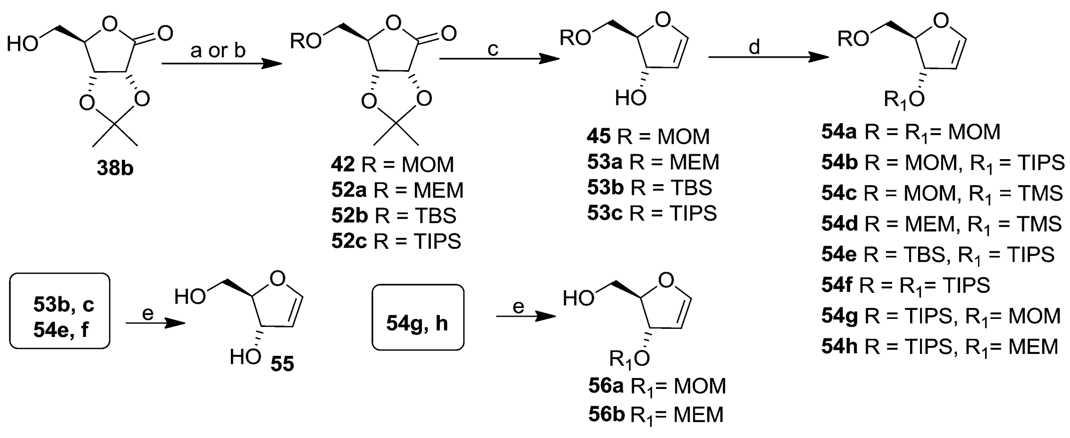
[a] 35 equiv. of metal, 0.5 M, 1 : 10 THF/NH$_3$, −78 °C, 30 min, then NH$_4$Cl. [b] 2 equiv. 0.07 M THF, 25 °C, 3 h. [c] 6 equiv. 0.21 M THF, −35 °C, 20 min, then H$_2$O. [d] 5 equiv. 0.50 M THF, 25 °C. [e] 5 equiv. 0.25 M THF, 25 °C. [f] 5 equiv. 0.25 M THF, −20 °C → 0 °C, 1 h, then H$_2$O. [g] 5 equiv. 0.20 M THF, −78 °C, 15 min, then H$_2$O. [h] No reaction.

ketene acetals **49** and **51**, derived from the furanoid glycal esters (**48**, **50**) by deprotonation with LDA in a 23 vol% mixture of hexamethylphosphoric triamide (HMPA) in THF or in 100% THF at −78 °C followed by silylation of enol ether with TMSCl (Scheme 8). Protected furanoid glycal **49** was further converted to natural product Lasalocid A (X537A) **174** after several steps (Schemes 31 and 33).

To obtain high yielding furanoid glycal **26**, they further extended their studies on reductive fragmentation of furanosyl chloride **32** with various reductants like metal/NH$_3$ systems, sodium napthalene and lithium di-*tert*-butylbiphenyl (Table 2) and found that lithium di-*tert*-butylbiphenyl afforded the furanoid glycal **26** in high yields (Scheme 9, Table 2).[19]

The same reaction protocol was latter followed by Daves *et al.* in 1985 to synthesize 3-hydroxy furanoid glycals (**45**, **53a–c**), and also a series of symmetrically (**54a**, **54f**) and differentially protected (**54b–e**, **54g**, **54h**) 3,5-bis-*O*-substituted furanoid glycals from 2,3-isopropylidene protected ribolactone **38b**. They also synthesized 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol **55** and 3-*O*-derivatized 5-hydroxy glycals **56** from their corresponding starting materials by removal of the silyl protecting groups (Scheme 10).[20a]

In the same year, Schlosser and coworkers described the synthesis of furanoid glycal of *threo* configuration from D-mannose (Scheme 11).[21] The free hydroxyl group at anomeric position of D-mannose **57** derived intermediate 1,2:5,6-di-*O*-



Scheme 10 Reagents and conditions: (a) To obtain **42** and **52a**: (i) MOMCl, ^{i}Pr$_2$EtN, DCM; (ii) MEMCl, ^{i}Pr$_2$EtN, DCM; (b) to obtain **52b** and **52c**: (i) TBSCl, imidazole, DMF; (ii) TIPSCl, imidazole, DMF; (c) ref. 4, 18 and 19; (d) ref. 20*a*; (e) ref. 20*b*.

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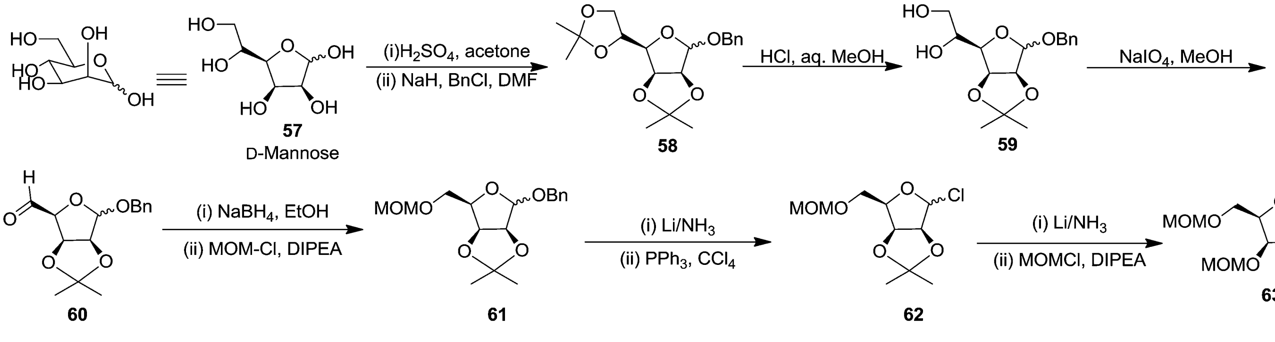


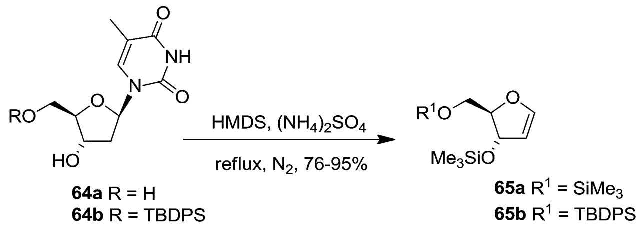
Scheme 11

isopropylidene-D-mannofuranose was benzylated with BnCl in the presence of NaH in dry DMF to afford benzyl protected compound **58** in good yield. The globally –OH protected compound **58** was treated with HCl in aq. MeOH to form diol **59** in 92% yield, which on treatment with $NaIO_4$ in 3 : 1 MeOH : H_2O mixture gave aldehyde **60** in 70% yield. Its reduction with $NaBH_4$ in EtOH followed by MOMCl protection of the resulting primary alcohol produced **61** in 89% yield. Its debenzylation with Li in liq. NH_3 followed by chloride formation with PPh_3 and CCl_4 in THF afforded **62** in 64% yield. Finally, it was reduced with Li/liq. NH_3 and the free 2° alcohol was protected with MOMCl to give *threo* furanoid glycal **63** in 56% yield (Scheme 11). It was utilized as key intermediate for the synthesis of *erythro*-(2*S*,3*R*)-sphingosine **232** which has been discussed in Scheme 39.

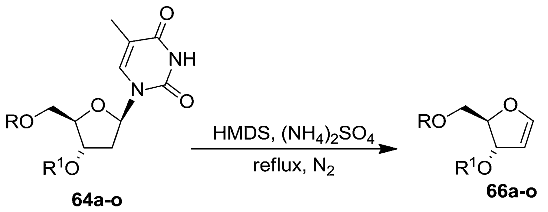
Pederson *et al.* reported the synthesis of *erythro* furanoid glycals from commercially available free thymidine **64a** or 5′-*O*-(*tert*-butyldiphenylsilyl)thymidine **64b** in a single step.[22] The nucleosides **64a** & **64b** were refluxed with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of $(NH_4)_2SO_4$ for 2 h under N_2 atmosphere to afford furanoid glycals **65a** & **65b** in 75–95% yields (Scheme 12).

This approach was further followed by Hammer *et al.* in 1997 to synthesize gram quantities of furanoid glycals (Scheme 13).[23] They synthesized wide range of *O*-silyl protected furanoid glycals. They also included 5′-ester (toluoyl) protected glycals as well as various combinations of 5′-ester and 3- and 5-TBS and TBDPS protected furanoid glycals (Table 3).

In 1994 Kassou and Castillón synthesized both *erythro* and *threo* furanoid glycals from easily available 2-deoxyribose **67** by using a key selenoxide elimination.[24] Methyl furanoside **68** was easily synthesized from 2-deoxyribose **67** by reaction with HCl/MeOH (0.05%), which was benzylated with BnBr/NaH to obtain **69a**. Similarly compounds **69b** and **72** were prepared by treating methyl furanoside **68** with PivCl and TBDPSCl respectively. The methyl 2-deoxy furanosides **69a**, **69b** and **72** were treated with PhSeH and BF_3/Et_2O to afford phenyl-2-deoxy-1-selenofuranosides **70a**, **70b** and **73** (α/β mixtures) in 85%, 71% and 75% yields respectively. For the synthesis of *threo* furanoid glycals, inversion of the 3-OH in compound **73** was achieved by its treatment with Tf_2O/Py followed by KNO_2/18-crown-6/DMF to afford *threo* derivative **74a** in 75% yield for the two steps (Scheme 14). Protection of the secondary alcohol with TBSCl led to compound **74b**. Treatment of **74a** with



Scheme 12



Scheme 13

Table 3 Product yields for furanoid glycals

Thymidine	Glycal	R	R^1	Yield (%)	Yield (%) from **64a**[a]
64a	**66a**	H	H	80	80(1)
64b	**66b**	TBDPS	H	91	70(2)
64c	**66c**	TBS	H	74	53(2)
64d	**66d**	Tol	H	52	38(2)
64e	**66e**	TBS	TBS	69	47(2)
64f	**66f**	TBDPS	TBDPS	80	76(2)
64g	**66g**	Tol	Tol	No glycal	No glycal
64h	**66h**	TBS	TBDPS	79	55(3)
64i	**66i**	TBS	Tol	No glycal	No glycal
64j	**66j**	TBDPS	TBS	59	40(3)
64k	**66k**	TBDPS	Tol	No glycal	No glycal
64l	**66l**	Tol	TBS	74	39(3)
64m	**66m**	Tol	TBDPS	94	64(3)
64n	**66n**	H	TBS	36	18(4)
64o	**66o**	H	TBDPS	79	53(4)

[a] The number in parentheses indicates the number of steps required to prepare the glycal from commercially available free thymidine **64a**.

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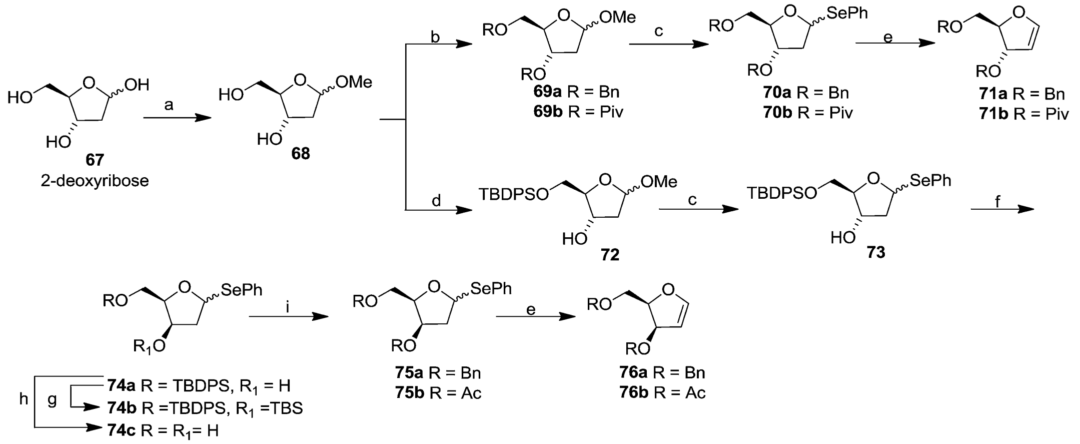


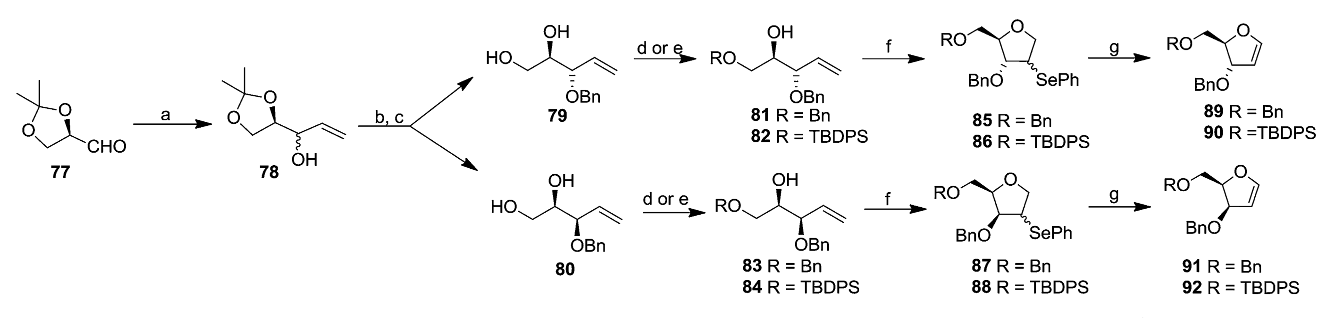
Scheme 14 Reagents and conditions: (a) HCl/MeOH (0.05%); (b) (i) BnBr. NaH, THF (**69a**); (ii) PivCl, Py (**69b**); (c) PhSeH, BF_3/Et_2O, DCM, −5 °C (**70**, **73**); (d) TBDPSCl/Im/DMF **72**; (e) $^iPr_2EtN$/*t*BuOOH/Ti(O-^{i}Pr)$_4$ (1 : 1 : 1), DCM, 0 °C; (f) (i) Tf_2O, Py, 0 °C. (ii) KNO_2, 18-crown-6, DMF; (g) TBSCl, DBU, benzene; (h) *n*Bu_4NF, THF; (i) (i) BnBr. NaH, THF (**75a**), (ii) Ac_2O, py (**75b**).

nBu_4NF led silyl deprotection to give **74c** whose phenylseleno derivatives **75a** and **75b** were easily obtained by usual benzyl and acyl protections respectively. Oxidation followed by thermal elimination of these phenyl-2-deoxy-selenofuranosides **70a**, **70b** and **75a**, **75b** with $^iPr_2EtN$/*t*BuOOH/Ti(O-^{i}Pr)$_4$ (1 : 1 : 1) system in DCM at 0 °C afforded corresponding furanoid glycals **71a**, **71b** and **76a**, **76b** in good yields.

Their work was further continued to synthesize differently protected *erythro* and *threo* furanoid glycals from 4-pentene-1,2,3-triol involving selenium induced *5-endo-trig* cyclization followed by selenoxide elimination.[25] They utilized inexpensive D-mannitol derived D-glyceraldehyde **77** as the starting material which on treatment with vinylmagnesium chloride in ether/THF furnished the alcohol **78** (1 : 1 mixture). Benzylation of free hydroxyl group followed by isopropylidene deprotection afforded separable diols **79** and **80.** The primary hydroxyl group of compounds **79** and **80** were selectively protected with BnBr *via* the stannylidene procedure to give alcohols **81** and **83.** In another set of experiments, **79** and **80** were selectively protected with TBDPSCl to obtain their respective alcohols **82** and **84** (Scheme 15). The protected alkenic alcohols **81–84** on treatment with *N*-phenylselenophthalimide (*N*-PSP) in the presence of CSA in DCM preferencially gave α/β mixture of 4-phenylselenenyl tetrahydrofurans **85–88** in different ratio through unusual *5-endo-trig* cyclization. These were oxidised with (*t*BuOOH, $^iPr_2EtN$, Ti(O-^{i}Pr)$_4$ in DCM) to obtain the corresponding selenoxides, which on prolong heating in DCM or DCE gave isolated *erythro* furanoid glycals (**89, 90**) and *threo* furanoid glycals (**91, 92**) respectively in good yields.

They further extended their work to synthesize differently protected *erythro* and *threo* furanoid glycals by oxidative elimination of 1-phenylselenenyl furanosides and 2-phenylselenenyl-1,4-anhydroalditol in the presence of *t*BuOOH, Ti(O-^{i}Pr)$_4$ and $^iPr_2EtN$ system.[26]

In 1995 Florent and co-workers reported the synthesis of 2′-*C*-acetoxymethylfuranoid glycal **97a** by reductive elemination of glycosyl phenyl sulfone **96** with SmI_2-HMPA,[27] which was obtained in four steps as discussed below from readily available α-D-isosaccharino-1,4-lactone **93** (Scheme 16). The sequential reduction-acetylation of the lactone **93** afforded peracetyl derivative **94**, which on treatment with PhSH/BF_3–Et_2O/DCM gave thiophenyl glycoside **95.** Its oxidation with *m*-CPBA produced phenyl sulfone **96** whose reductive samariation with SmI_2 in THF in the presence of HMPA, followed by elimination of the acetate, afforded the furanoid glycal **97a.** It was then converted into **97b** *via* a six membered cyclic



Scheme 15 Reagents and conditions: (a) vinylmagnesium chloride, ether/THF; (b) NaH, BnBr; separation of isomers; (c) H $^+$, MeOH; (d) to obtain **81** and **83** (i) Bu_2SnO, toluene, 4 Å MS; (ii) BnBr, Bu_4NBr; (e) to obtain **82** and **84**: TBDPSCl, imidazole, DMF; (f) *N*-PSP, CSA, DCM; (g) *t*BuOOH (2.5 equiv.), $^iPr_2EtN$ (1.7 equiv.) and Ti(O-^{i}Pr)$_4$, (1 equiv.) in DCM (48 h) or DCE (4 h), reflux.

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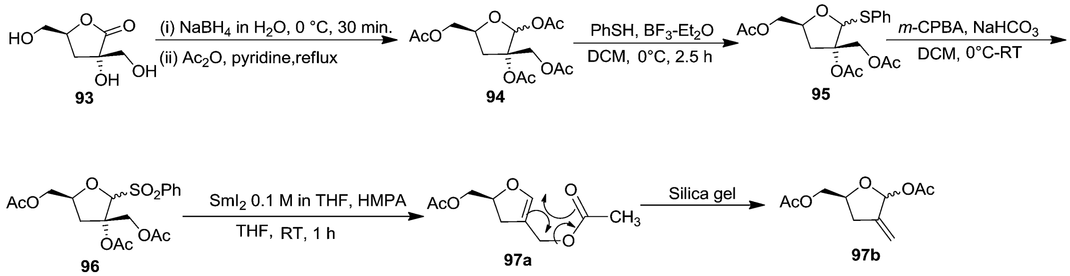


Scheme 16

rearrangement during purification by silica gel column chromatography. The formation of *N*-nucleosides 2′,3′-dideoxy-2′-*C*-methylidene-5-methyl uridine **623** and 3′-deoxy analog of DMDC **626** and **627** from furanoid glycal **97a** has been discussed in Scheme 105.

In 1996 Townsend *et al.* synthesized ribofuranoid glycals in multigram scale from 2-deoxy-ribose derived 2-deoxy-D-ribono-1,4-lactone **98**,[28] which was bis-silylated at 3- and 5-positions with different silyl chloride in DMF in the presence of imidazole to give the 3,5-bis-*O*-silylated products **99a–c**. These silyl protected compounds **99a–c** were reduced with DIBALH at −78 °C to their corresponding 2-deoxy-D-*erythro*-pentofuranose derivatives **100a–c** (α/β = 1 : 1). Its mesylation followed by *in situ* elimination of MsOH furnished ribofuranoid glycals **102a–c** (Scheme 17).

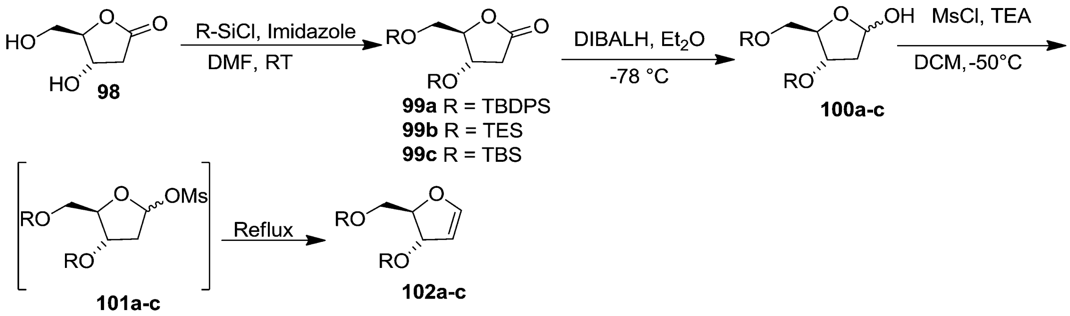
Furanoid glycals were also synthesized by McDonald and Gleason through trialkylamine-molybdenum pentacarbonyl-catalyzed alkynol *endo* cycloisomerizations,[29] which were easily prepared in chiral nonracemic form by short synthetic sequences featuring asymmetric epoxidations of commercially available allylic alcohols (Schemes 18 and 19).

Furanoid glycal **106** was prepared by asymmetric epoxidation of allyl alcohol **103** followed by *in situ* esterification with pivaloyl chloride to give **104** (Scheme 18). Regioselective addition of LiC≡CH/BF$_3$·Et$_2$O to **104** at low temperature (−78 °C to −20 °C) provided the homopropargylic secondary alcohol **105.** Treatment of **105** with Mo(CO)$_6$ and trimethylamine-N-oxide in ether/Et$_3$N at room temperature gave **106** in 80% isolated yield (Table 4).[29]

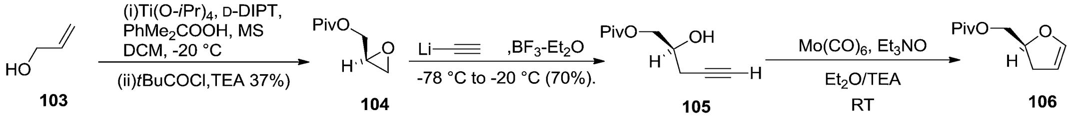
They also reported the asymmetric synthesis of alkynols having propargylic nitrogen substituents. These substrates were prepared from (*E*)-2-penten-4-yn-1-ol **107** (Scheme 19). Asymmetric epoxidation of **107** furnished **108** which on treatment with Ti(O-^{i}Pr)$_2$(N$_3$)$_2$ in toluene followed by the selective protection of the resulting primary alcohol **109** formed the azide **110.** Its reduction with tin(II) chloride in MeOH yielded the amine **111** which was acylated with Ac$_2$O and Tf$_2$O to obtain the respective 3-amidoalkynols **112** and **113** respectively.

The various alkynols were subjected to Mo-catalyzed alkynol cyclization to obtain furanoid glycal and THF derivatives as shown in Table 4.

Here it is worth mentioning that the Mo-catalyzed alkynol cyclization method was compatible with alkynol substrates containing propargylic nonbasic, ester and amide functional groups (**105, 116, 112, 113**) for synthesis of furanoid glycals (**106, 117, 121, 122**). Whereas, alkynol substrates bearing good leaving groups (*i.e.*, N$_3$ group) and basic groups (*i.e.* NH$_2$, OR) at



Scheme 17



Scheme 18

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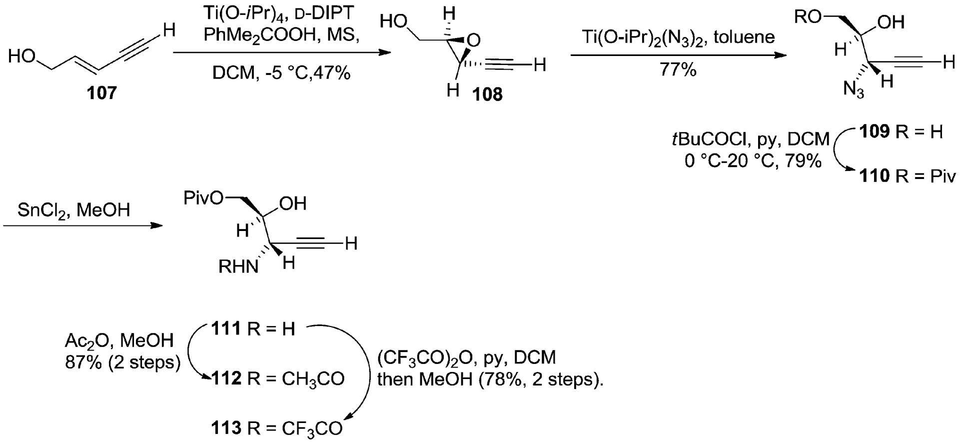
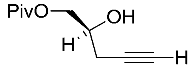
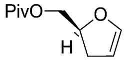
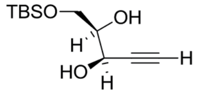
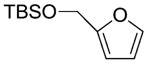
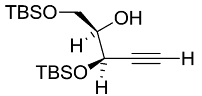
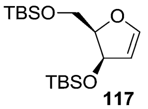
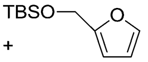
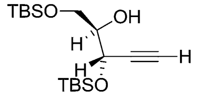
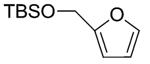
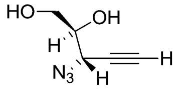
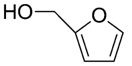
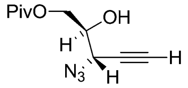
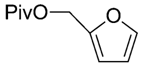
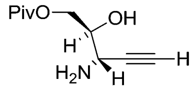
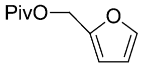
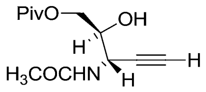
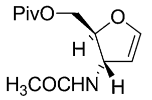
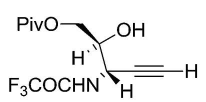
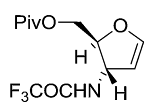
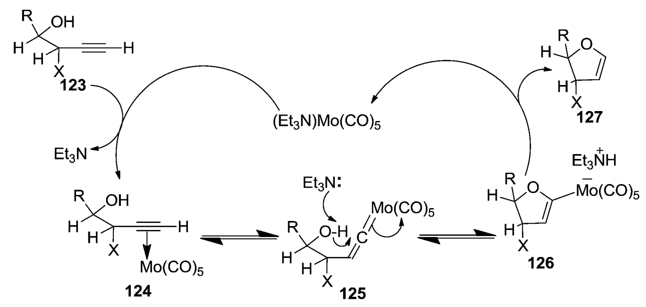


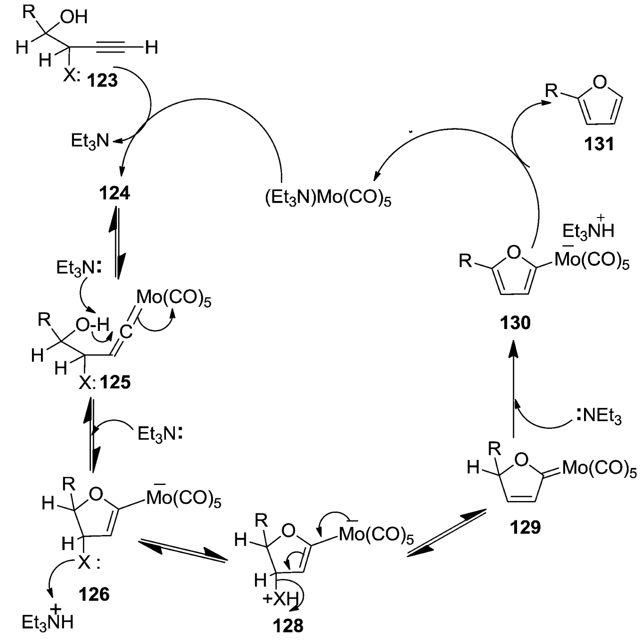
Scheme 19

Table 4 Cyclization of alkynols with trialkylamine-molybdenum pentacarbonyl

Alkynols	Products (isolated yields)
 **105**	 **106**
 **114**	 **115**
 **116**	 **117** +  **115**
 **118**	 **115**
 **109**	 **119**
 **110**	 **120**
 **111**	 **120**
 **112**	 **121**
 **113**	 **122**



Scheme 20 Mechanism for alkynol cycloisomerization (X= non basic group, H, NH(CO)R).



Scheme 21 Mechanism for furan formation (X = N_3, or basic groups *i.e.* NH_2, OR).

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the propargylic position (**114**, **118**, **109**, **110**) underwent cyclization followed by elimination afforded furan derivatives (**115**, **119**, **120**). The mechanistic explanations for their formation are delineated below (Schemes 20 and 21). These furanoid glycals further utilized for synthesis of deoxynucleosides (Schemes 106–111).

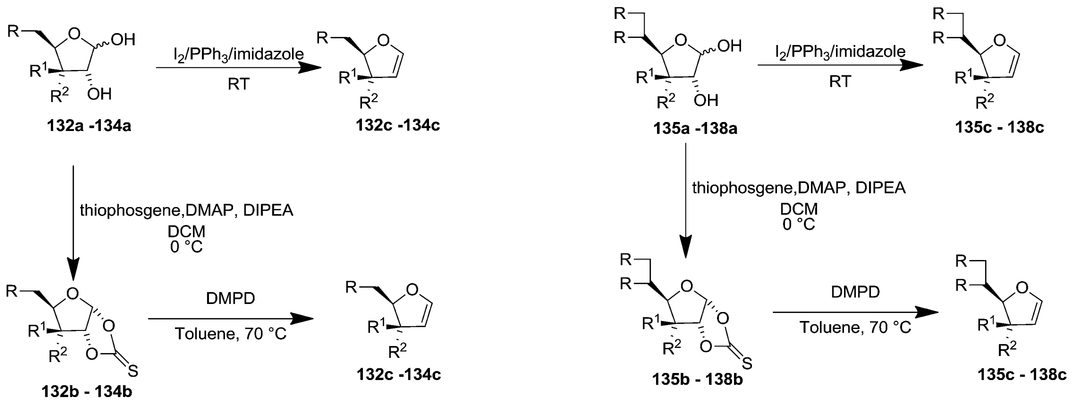
In 1997 Diaz *et al.* described two synthetic procedures for *C*-3,4-D-*threo* and D-*erythro* furanoid glycals from protected 1,2-dihydroxy pento- and hexo-furanose derivatives with the D-*xylo*, D-*gluco* and D-*ribo*, D-*allo* configurations as starting materials.[30]

The first one referred to the Garegg-Samuelsson reaction on *vic*-diols (**132a–138a**) in the presence of I_2-PPh_3-Im caused substitution followed by elimination of unstable *vic*-diiodide intermediate to the corresponding furanoid glycals (**132c–138c**) (Scheme 22).

The second one was modified Corey's dideoxygenation of 1,2-thiocarbonates (**132b–138b**) which were derived from the reaction of 1,2-diols (**132a–138a**) with thiophosgene in alkaline medium in good yields. These 1,2-thiocarbonates (**132b–138b**) on treatment with 1,3-dimethyl-2-phenyldiazaphospholidine (DMPD) in dry toluene at 70 °C underwent elimination to give furanoid glycals (**132c–138c**) (Scheme 22).

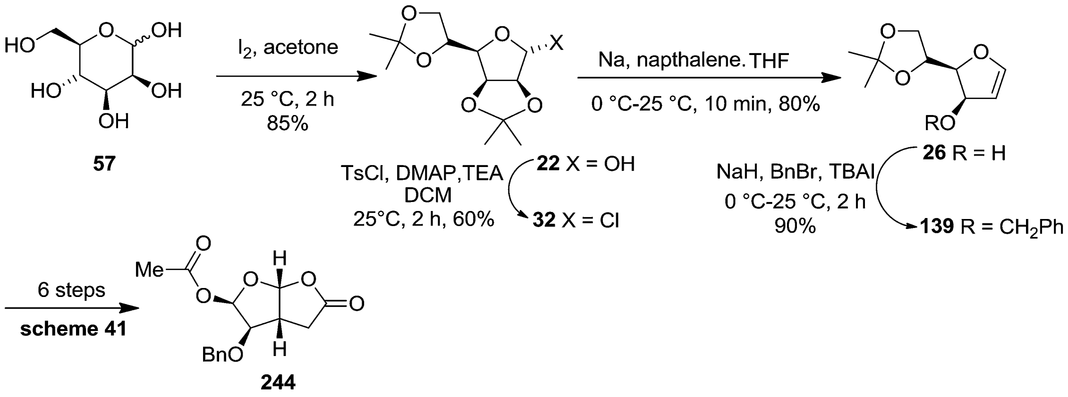
In 1999 Theodorakis and co-workers disclosed a short and efficient enantioselective synthesis of norrisane side chain **244** from furanoid glycal **139** (Scheme 41) derived from D-mannose **57**.[31] They followed Ireland's method to synthesize furanoid glycal **139** from D-mannose **57** in good yield. D-Mannose **57** was treated with acetone in presence of iodine as a catalyst to deliver bis-acetonide **22** in 85% yield, after a simple filtration and crystallization. Its treatment with *p*-TsCl and Et_3N afforded glycosyl chloride **32**, which upon slow addition to a stirring mixture of sodium naphthalenide in THF gave furanoid glycal **26** in 48% overall yield (for two steps). Due to its labile nature, it was immediately benzylated (BnBr, NaH, TBAI) to produce the glycal **139** in 90% yield (Scheme 23) which was utilized to achieve the synthesis of norrisane side chain **244** in 6 steps discussed in Scheme 41.

In 2000, Knaus *et al.* reported the synthesis of analogues of deoxy-β-L-cytidine *via* furanoid glycal as key intermediates. They followed Garegg Samuelsson reaction for the synthesis



132 and **135** R= R^1 = OBn; R^2 = H
133 and **136** R = R^1=OBz; R^2 = H
134 R = OPiv; R^1= H; R^2 = OBz
137 R = OBz; R^1 = OAll; R^2 = H
138 R =R^2 = OBz; R^1 = H

Scheme 22



Scheme 23

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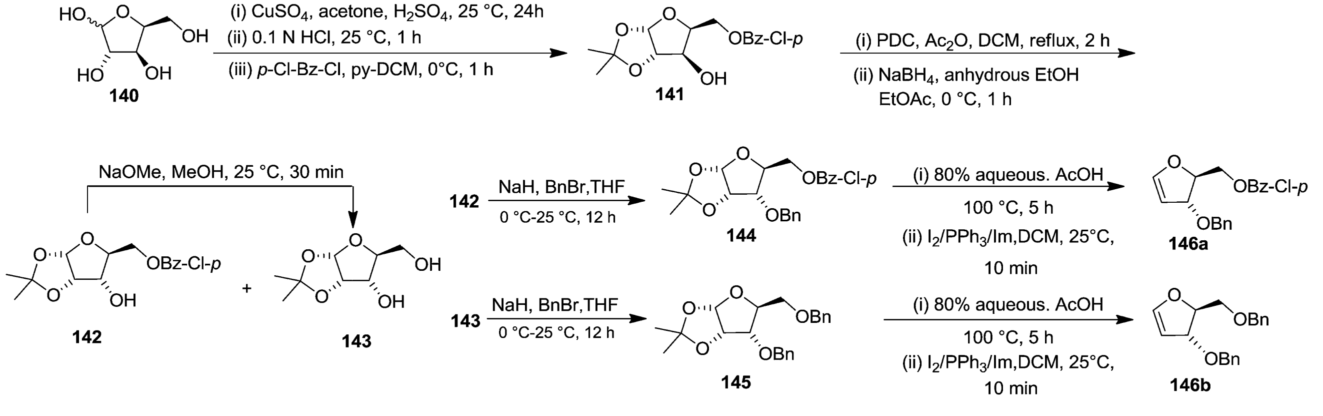
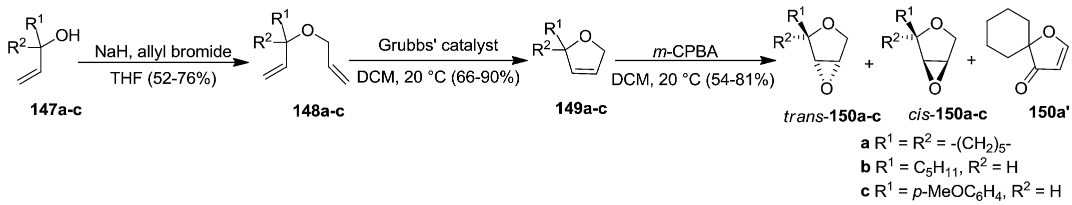


Scheme 24

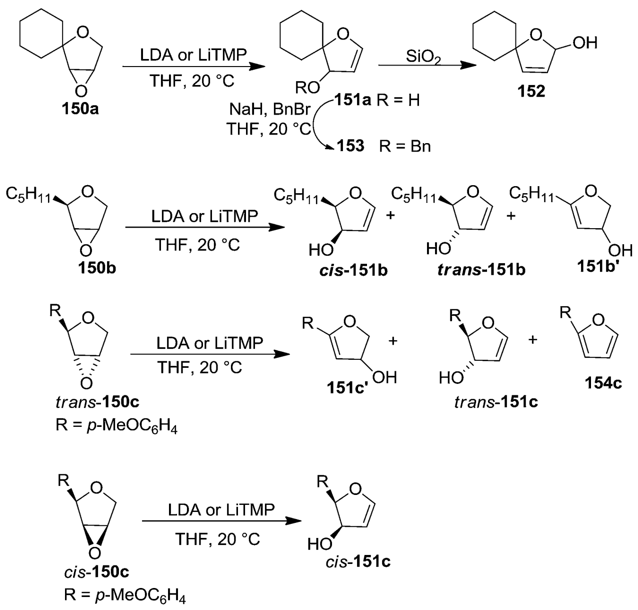


Scheme 25

of ribo furanoid glycals from *vic*-diols intermediate, easily derived from L-xylose **140**.[32] Acetonide protection of L-xylose **140** followed by selective acid hydrolysis with 0.1 N HCl afforded intermediate 1,2-*O*-isopropylidene-α-L-xylofuranose whose primary hydroxyl group was selectively protected with *p*-Cl-Bz-Cl in pyridine-DCM at 0 °C to obtain **141**. Its free hydroxyl group was oxidised with PDC in DCM, and the resulting ketone was reduced with $NaBH_4$ to afford a mixture of ribose derivatives **142** (68% yield) and **151** (28% yield). The sugar derivative **142** was converted into compound **143** with NaOMe in MeOH. It was benzylated with BnBr in THF in the presence of NaH to afford the 3,5-di-*O*-benzyl-L-ribose derivative **145** in good yields. The similar protocol was adopted to obtain the 5-*O*-(*p*-chlorobenzoyl)-3-benzyl-L-ribose derivative **144** from its precursor **142**. The 1,2-*O*-isopropylidenyl groups in **144** and **145** were readily removed by treating each with 80% aqueous AcOH at 100 °C to give the *vic*-diols. Their debenzylation with the I_2-PPh_3-Im system in dry DCM at 25 °C afforded the desired ribofuranoid glycals **146a** and **146b** in 62% and 45% yield respectively (Scheme 24). These were used as key intermediates for synthesis of unnatural C-aryl 2′-deoxy-β-L-cytidine mimics (**529a, b**) (Scheme 92).

In the same year Schmidt and Wildemann developed the synthesis of 2,3-dihydropyrans or 2,3-dihydrofurans (furanoid glycals) utilizing ring closing methathesis as one of the key reaction steps. The allylic alcohols (**147a–c**) were subjected to allylation with allyl bromide in the presence of NaH in THF to obtain the diallyl ethers (**148a–c**). Their ring-closing metathesis yielded 3,4-dihydrofurans (**149a–c**) followed by their epoxidation with *m*-CPBA gave dihydrofuran oxides (**150a–c**). In the case of **150a**, spiro dihydrofuranone **150a′** was obtained along with *cis*, *trans*-**150a** (Scheme 25).[33]

The base-induced rearrangement of **150a** with LDA in THF at ambient temperature gave a crude product whose NMR spectra identified it as **151a**. It was rearranged to hemiacetal **152** during its silica gel column purification. However, this was supressed when free hydroxyl group in **151** was protected as a benzyl ether **153** (Scheme 26).



Scheme 26

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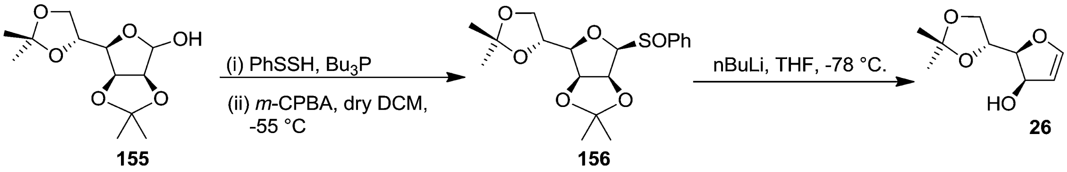
The rearrangement of inseparable diastereoisomeric mixture of dihydrofuran oxide **150b** underwent the rearrangement reaction with LDA or LiTMP to give a 4 : 3 : 1 mixture of isomers *cis*-**151b**, *trans*-**151b** and **151b′** which were characterized by NMR spectroscopy of crude reaction mixture.

The dihydrofuran oxides *trans*- and *cis*-**150c** were separable. While the treatment of *trans*-**150c** with LiTMP gave three products in a ratio of 9 : 3 : 1 which were identified as furanoid glycals **151c′**, *trans*-**151c** and furan **154c**, the *cis*-**150c** yielded only one rearrangement product *cis*-**151c**.

Recently the furanoid glycal **26** was synthesised by Gómez and López *et al.* from **155**. Its thioglycosylation followed by controlled oxidation of the resulting thioglycoside with *m*-CPBA afforded furanosyl sulfoxide **156** which on treatment with *n*BuLi furnished column pure furanoid glycal **26** in good yield (Scheme 27).[34]

As mentioned above, several methods are available for synthesis of furanoid glycals or 4,5-dihydrofurans but difficulties are generally encountered with the formation of unstable glycals,[13] usage of expensive starting materials[22,23] and, in some cases, low yield of the desired products and that is why improvements in the existing methods are still desirable. To overcome all these limitations and encouraged by the literature reports on various applications of furanoid glycals in organic synthesis, our research group reported a simple protocol for the synthesis of stereochemically pure different furanoid glycals **162a** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-L-arabino-hex-1-enitol), **162b** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-L-*ribo*-hex-1-enitol), **162c** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-D-*ribo*-hex-1-enitol),[17a] **139** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-D-arabino-hex-1-enitol)[17a,31,36,37] and also highly functionalized 2,5-dihydrofurans (**163a, b**) (Fig. 3) from easily accessible



Scheme 27

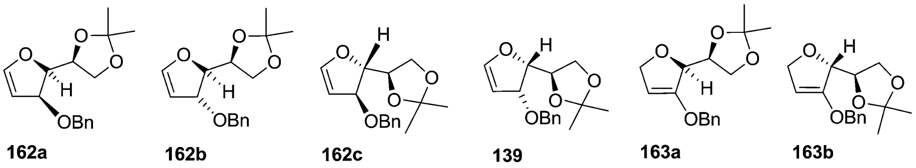
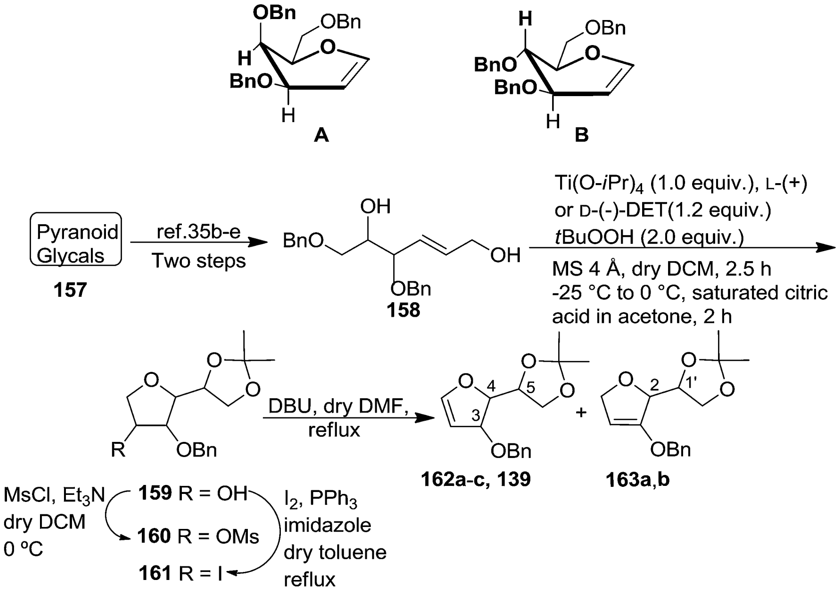


Fig. 3 Structures of furanoid glycals (**162a–c**, **139**) and highly functionalized 2,5-dihydrofurans (**163a**, **b**).



Scheme 28 General strategy for the synthesis of furanoid glycals (**162a–c**, **139**) and functionalized 2,5-dihydrofurans (**163a**, **b**).

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enantiomerically pure 2,3,4-trisubstituted THF scaffolds (**159a–d**).[35] To the best of our knowledge, examples for the synthesis of enantiomerically pure furanoid glycals (**162a, b**) and functionalized 2,5-dihydrofurans (**163a, b**) had not been reported.[35a]

The synthetic protocol to obtain a family of furanoid glycals (**162a–c, 139**) of different configurations at the 3-, 4- and 5-positions and functionalized 2,5-dihydrofurans (**163a, b**) of different configurations at the 2- and 1′-positions from enantiopure THF scaffolds (**159a–d**) is shown in Scheme 28. These

Table 5 Synthesis of furanoid glycals (**162a–c**, **139**) and functionalized 2,5-dihydrofurans (**163a**, **b**) from mesyl derivatives (**160a–d**)

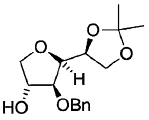
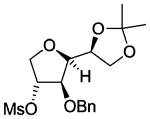
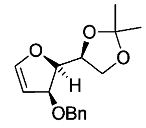
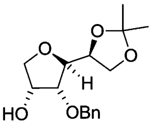
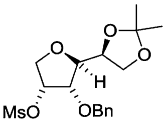
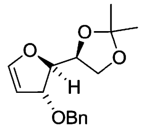
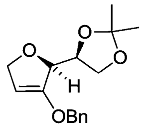
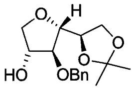
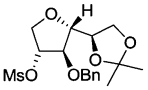
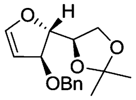
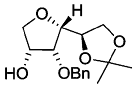
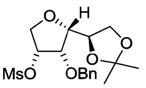
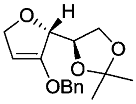
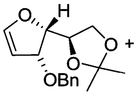
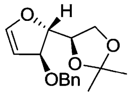
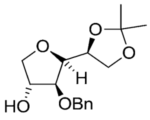
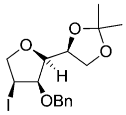
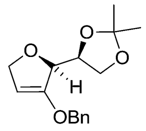
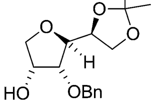
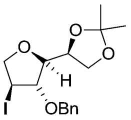
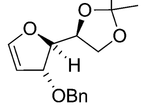
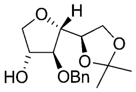
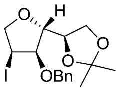
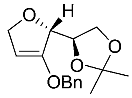
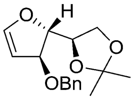
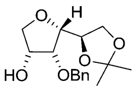
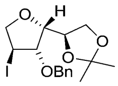
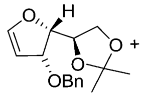
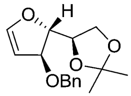
Entry	THF domains (**159a–d**)	Mesyl derivatives (**160a–d**)	Major products	Minor products
1	 **159a**	 **160a**	 **162a** (52%)	—
2	 **159b**	 **160b**	 **162b** (34%)	 **163a** (19%)
3	 **159c**	 **160c**	 **162c** (52%)	—
4	 **159d**	 **160d**	 **163b** (61%)	 +  **139** **162c** inseparable mixture 5% **139:162c = 1:0.2 from ^{1}H NMR**

Table 6 Synthesis of furanoid glycals (**162a–c**, **139**) and functionalized 2,5-dihydrofurans (**163a**, **b**) from Iodo derivatives (**161a–d**)

Entry	THF domains (**159a–d**)	Iodo derivatives (**161a–d**)	Major products	Minor products
1	 **159a**	 **161a**	 **163a** (67%)	—
2	 **159b**	 **161b**	 **162b** (54%)	—
3	 **159c**	 **161c**	 **163b** (64%)	 **162c** (29%)
4	 **159d**	 **161d**	 +  **139** **162c** inseparable mixture 67% **139:162c = 1:0.2 from ^{1}H NMR**	—

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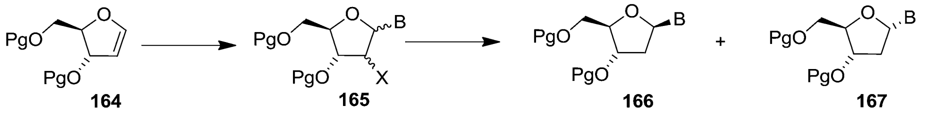
THF scaffolds (**159a–d**) were prepared from Pyranoid glycals (**157**) (3,4,6-tri-*O*-benzyl-D-galactal (**A**) and 3,4,6-tri-*O*-benzyl-D-glucal (**B**)) derived allylic alcohols (**158**) involving the intramolecular asymmetric ring opening (ARO) of the enantiomerically pure 2,3-epoxy alcohols using Sharpless asymmetric epoxidation (SAE) conditions followed by subsequent isopropylidene protection of the diol. The free hydroxyl group in **159** was protected with MsCl in the presence of Et$_3$N to afford the corresponding mesyl derivative **160**. The OMs protected THF **160** in dry DMF was subjected to thermal elimination reaction for 8 h in the presence of DBU to furnish the furanoid glycals (**162a–c**, **139**) and 2,5-dihydrofurans (**163a**, **b**). These furanoid glycals and 2,5-dihydrofurans were obtained in good yields when the stereochemically inverted iodides **161**, prepared by Garegg–Samuelsson reaction (I$_2$/PPh$_3$/imidazole) from **159**, were heated at reflux with DBU in dry DMF for 5 h (Scheme 28, Tables 5 and 6).[35a]

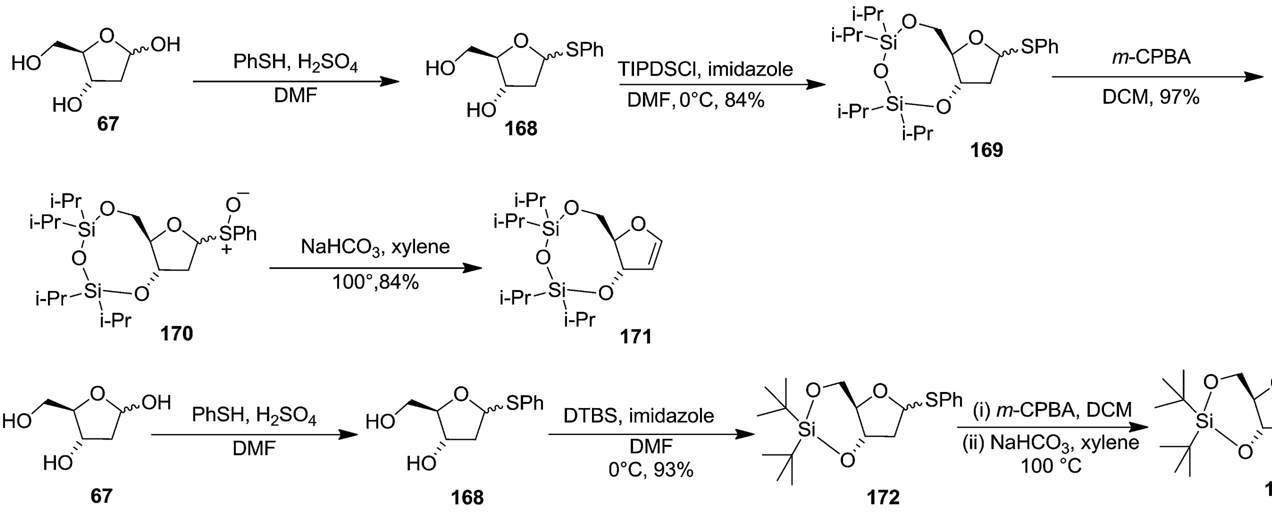
The construction of the double bonds was accomplished here by carrying out a base-induced E2 elimination of enantiomerically pure C4 mesylate or iodo THF scaffolds (**160** or **161**) by utilizing inexpensive reagents with a simple experimental and workup procedure. In the formation of either glycal or olefin, the E2 elimination took place most readily when the hydrogen atom and the leaving group were in an antiperiplanar arrangement. Further, it can be argued that E2 elimination of MsOH from **160b** leading to the formation of two products in which furanoid glycal **162b** (Hofmann product) was formed predominantly over Saytzeff product **163a** (more substituted olefin) may be attributed to the involvement of a conformation in which the leaving group, 4-OMs, and one of the hydrogen atoms at C5 adopted a relatively higher degree of antiperiplanar arrangement relative to the antiperiplanar arrangement of 4-OMs and H3. In contrast, the formation of Saytzeff product **163b** as the major product and a mixture of glycals (**162c**, **139**) as the minor product, both from **160d**, could be attributed to the comparable torsion angles subtended by the OMs group and the H atom across the C4–C3 and C4–C5 bond, respectively. Similarly, E2 elimination of HI from **161c** gave expected Saytzeff product **163b** as the major product over furanoid glycal **162c** as a result of the same reason described in the case of E2 elimination of MsOH from **160d**. We also showed that furanoid glycals **162a** and **162c** or functionalized 2,5-dihydrofurans **163a** and **163b** can be synthesized exclusively or in major quantity from the same 2,3,4-trisubstituted THF scaffolds **159a** and **159c**, respectively, by changing the leaving group at C4. Furthermore, this report provided two pairs of enantiomeric furanoid glycals (4,5-dihydrofurans) (**162a**, **139**) and (**162b**, **162c**) and one pair of enantiomeric 2,5-dihydrofurans (**163a**, **163b**) (Fig. 3).

In 2010, Haraguchi and group described electrophilic glycosidation of *erythro*-furanoid glycal **164** with nucleobases followed by removal of the substituent X at the 2′-position of the resulting product **165** to give a mixture of β-and α-2′-deoxynucleosides (**166**, **167**) (Scheme 29).[38]

To improve the β-selectivity, for the first time they reported the synthesis of *erythro*-furanoid glycals (**171**, **173**) by means of sulfoxide *syn*-elimination (Scheme 30). 2-Deoxy-D-ribose **67** on treatment with PhSH/H$_2$SO$_4$ in DMF afforded phenyl-2-deoxy-1-thio-D-*erythro*-pentofuranoside **168** in 97% yield. The free hydroxyl groups of **168** were silylated with TIPDSCl to give **169** in 84% yield. Its oxidation with *m*-CPBA led to the formation of the



Scheme 29



Scheme 30

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sulfoxide **170** in 96% yield. The sulfoxide **170** on treatment with solid $NaHCO_3$ in refluxing xylene underwent sulfoxide *syn*-elimination to furnish glycal **171** in 84% yield. Likewise, **168** was protected with the DTBS group to give **172** (93% yield), which was then converted to the 3,5-*O*-DTBS-protected glycal **173** in 83% yield by adopting the reaction sequence similar to that employed for the synthesis of glycal **171**. The synthesis of nucleosides utilizing these furanoid glycals (**171**, **173**) has been delineated in Schemes 128 and 129.

3. Applications of furanoid glycals

3.1. Synthesis of natural products and related compounds

Nowadays, for the synthesis and utilization of chiral building blocks (CBBs) for the synthesis of target molecules for drug design and enantiomerically pure simple and complex natural products are in great demand. This approach of synthesis utilizing the stereochemistry of the starting material is customarily known as the 'chiron' approach synthesis[39] and it becomes very cost effective if starting material is derived from inexpensive carbohydrate or amino acid.

The furanoid glycals derived from different starting materials have been utilized as chiral pool material by various groups for synthesis of variety of natural products and important target molecules, which are discussed below.

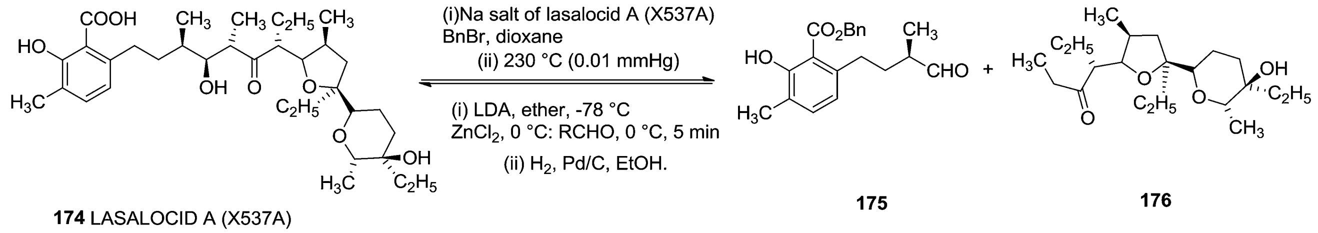
Ireland and group reported the total synthesis of Lasalocid A (X537A) **174** and analogues. For the synthesis of Lasalocid A (X537A)**174**, they described the construction of both the aldehyde **175** and ketone **176** available from the reverse aldol reaction of lasalocid A (X537A) **174** (Scheme 31).[40,41]

On the basis of a retrosynthetic strategy using the Ireland-Claisen rearrangement to form the two C-glycosides bearing chiral centres at the C-α positions, they utilized carbohydrate precursors as the source of the furanoid and pyranoid subunits for the construction of ketone **176** (Scheme 32).

First they tried the synthesis of **176** from furanoid glycal **45** which was converted to protected furanoid glycal **49** which is described in Scheme 8,[4] from which the isomeric mixture of acid **180** was prepared by [3,3] sigmatropic rearrangement at 35 °C.[4] This acid mixture **180** was converted to α-epoxides **182** in 90% overall yield through the intermediate iodolactone **181**. Treatment of **182** with lithiated 1,3-dithiane followed by desulfurization of the resulting products provided **183** in moderate yield. It was converted to acid **186** (epimer of **177**) *via* the intermediates **184** and **185** (Scheme 33).

They chose α-D-glucosaccharino-1,4-lactone **187** as the starting material for the purpose to synthesize **177**. It was converted to the mixture of unsaturated isomeric esters **190**. Hydrogenation of **190** yielded **191** and **192**, which were separated by column chromatography. After LAH reduction of **191** and **192**, both the resulting alcohols (**193**, **194**) were readily transformed to the acids **177** and **186** respectively (Scheme 34).

The construction of Pyranoid glycal **178** started with 6-deoxy-L-gulose **195** as shown in Scheme 35. The hydroxyl groups were differentiated as benzyl glycoside, *O*-isopropylidene, and methoxymethyl ether in compound **196**. Removal of the benzyl

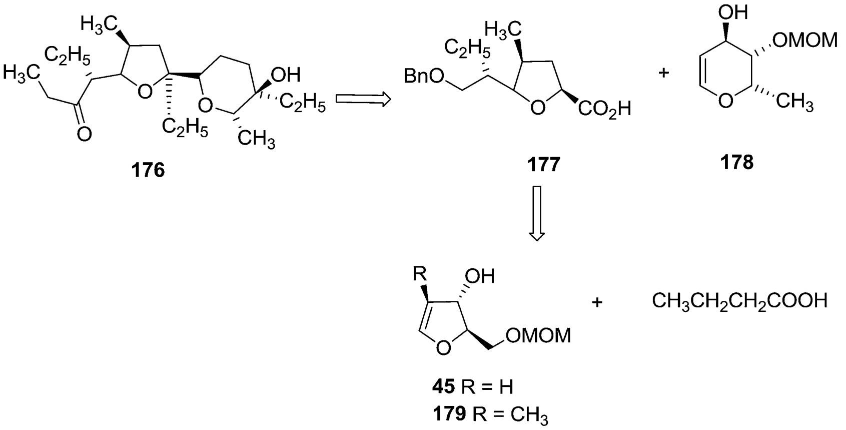


174 LASALOCID A (X537A)

175

176

Scheme 31



176

177

178

45 R = H
179 R = CH3

Scheme 32 Retro synthetic strategy for synthesis of ketone **176**.

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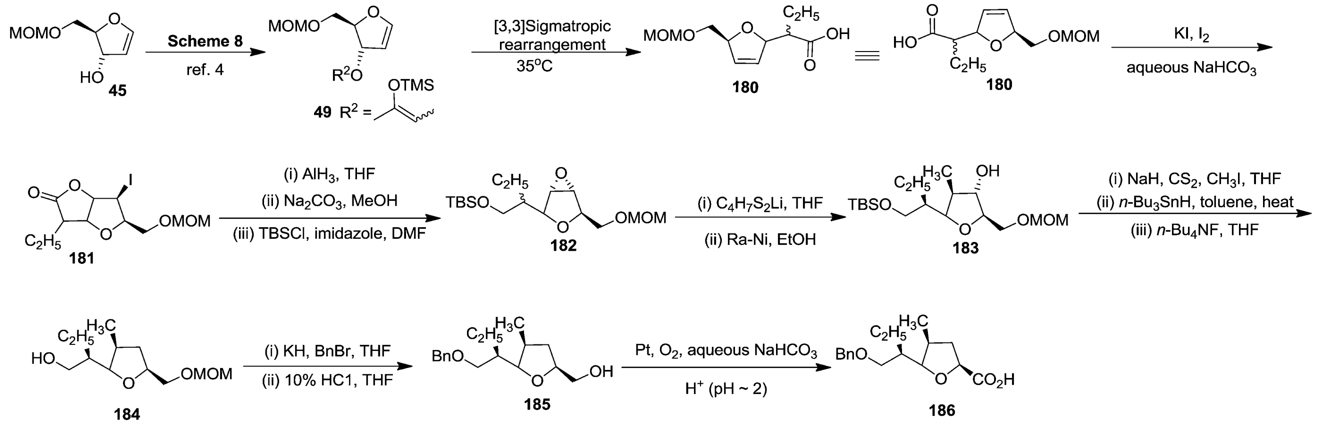
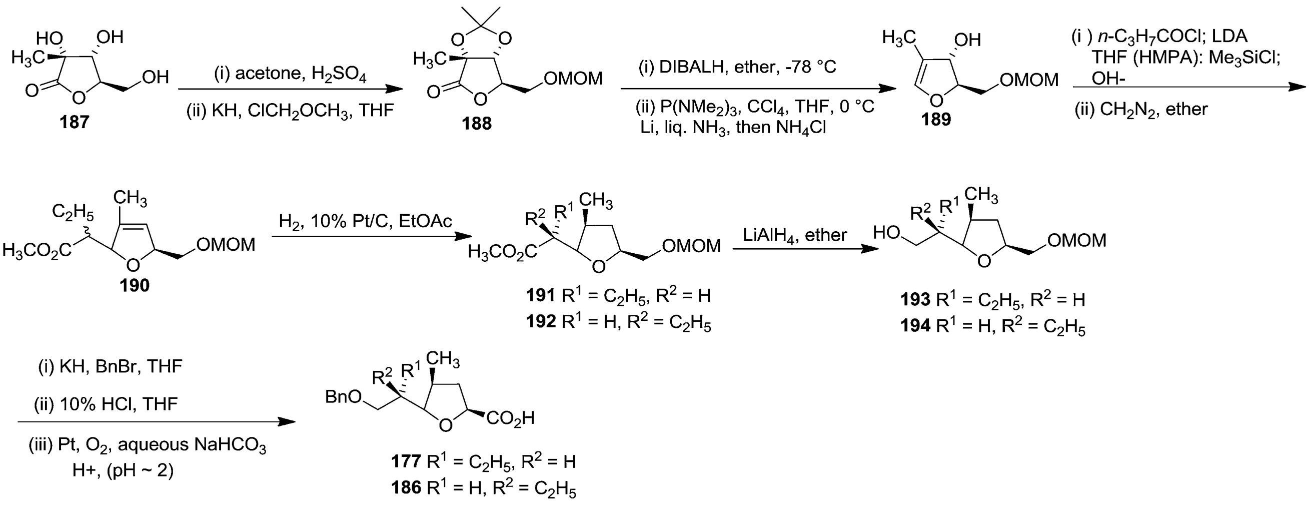
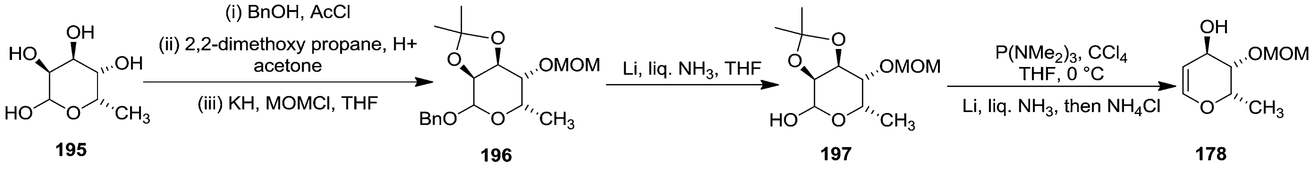


Scheme 33



Scheme 34



Scheme 35

ether then led to the lactol **197** which was converted to the desired glycal **178** by their optimised procedure (Scheme 35).

The connection of the pyranoid subunit **178** to acid **177** resulted in readily separable isomeric esters **198** and **199**, while the epimer **186** afforded the isomeric esters **200** and **201**. Subsequent transformation of these esters individually to alcohols **206–209** proceeded in excellent yields *via* **202–205** (Scheme 36).

Alcohol **207** was transformed into ketone **210**, which was converted to the *exo* methylene olefin followed by oxidation with *m*-CPBA afforded a mixture of epoxides in which the β-epoxide **211** was the major component. Subsequent reductive cleavage of this isomer then led to the tertiary alcohol **212** which was transformed into the aldehyde **213** involving sequence of reactions like debenzylation and oxidation of the resulting primary alcohol. Finally its Grignard reaction furnished the ketone **176** (Scheme 37). The aldol condensation between the aldehyde **175** and the zinc enolate of the ketone **176** completed the total synthesis of Lasalocid A (X537A) **174** (Scheme 31).

In 1980 Corey *et al.* synthesized 6-*epi*-leukotriene C or 6-*epi*-LTC **225** and 6-*epi*-leukotriene D or 6-*epi*-LTD **226** from D-mannose derived furanoid glycal **26.** First it was converted to

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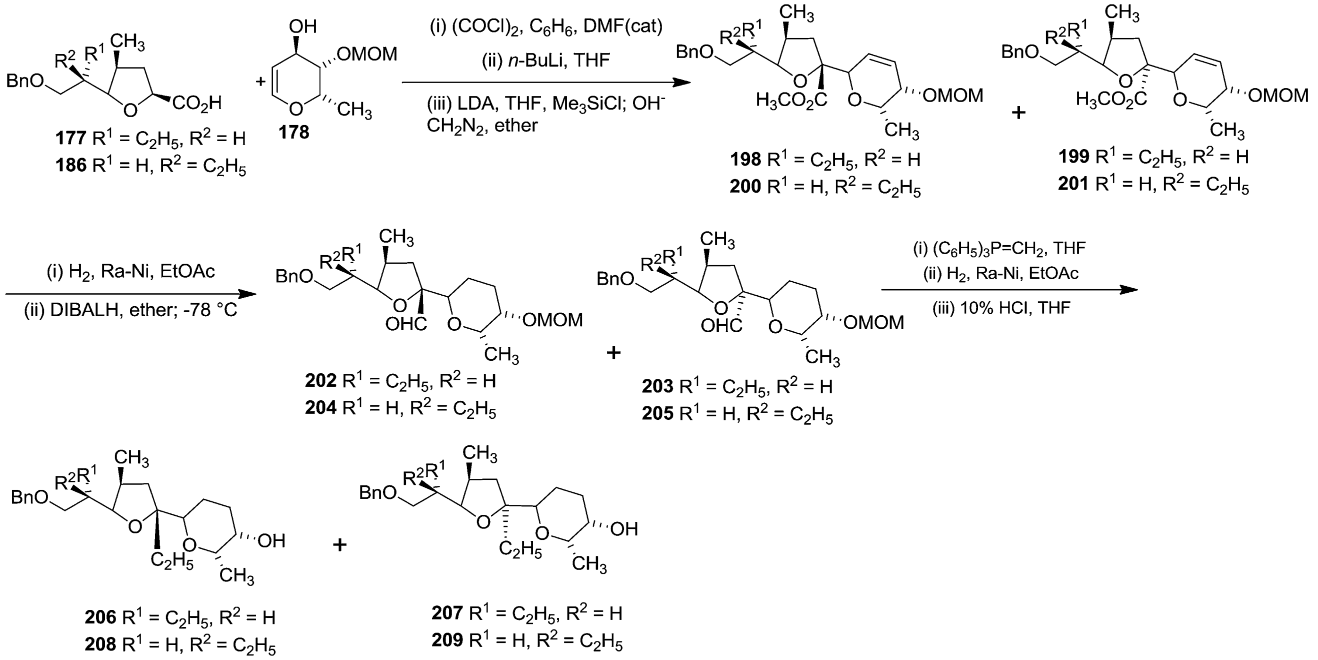
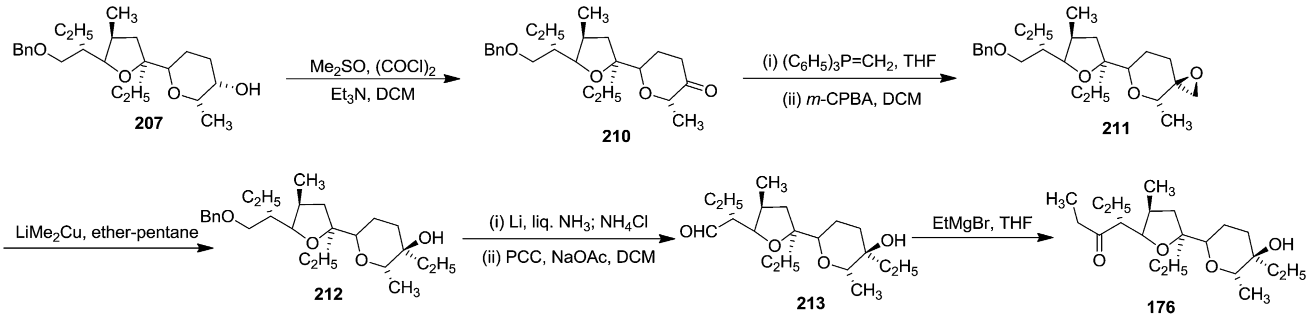
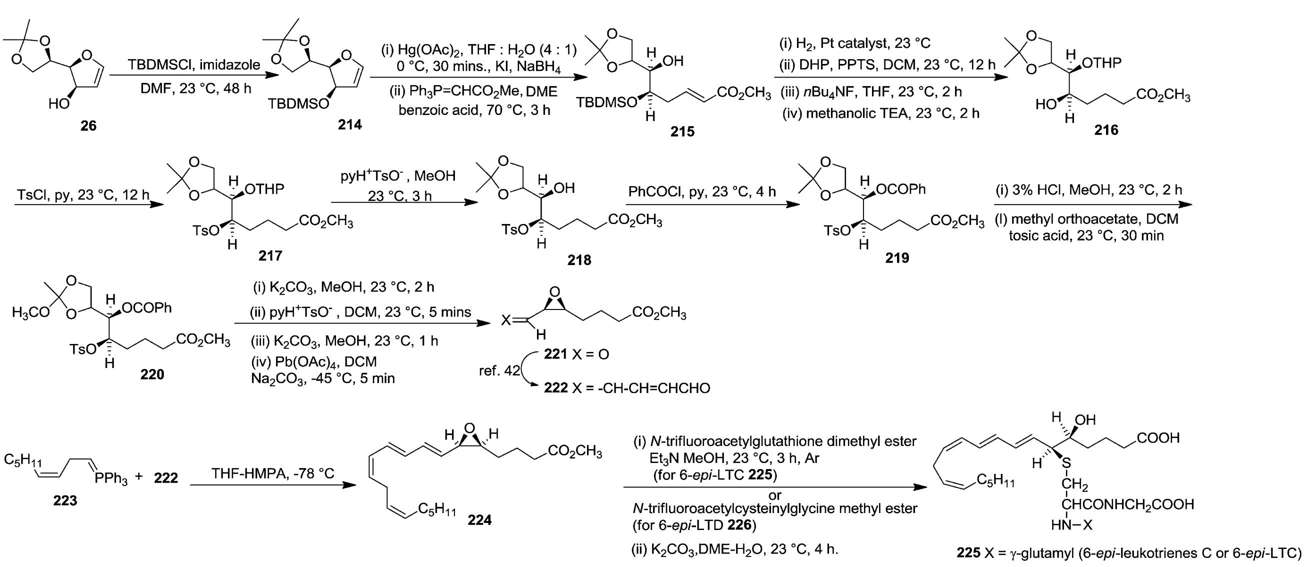


Scheme 36



Scheme 37



Scheme 38

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TBDMS ether derivative **214** by treatment with TBDMSCl, imidazole in dry DMF at 23 °C for 48 h (Scheme 38).[5,42] Its successive oxymercuration-demercuration reactions followed by esterification of the resulting hemiacetal with methoxycarbonylmethylenetriphenylphosphorane in DME containing a trace of benzoic acid at 70 °C for 3 h gave unsaturated ester **215** in 96% yield. Its sequential hydrogenation followed by tetrahydropyranylation and desilylation formed an intermediate δ-lactone which on treatment with methanolic triethylamine at 23 °C for 2 h provided hydroxy ester **216** (99% yield). Tosylation of **216** gave **217** in 97% yield. Deprenylation of **217** and benzoylation of the resulting **218** (92% yield) gave **219**. Acetonide deprotection followed by reaction of the corresponding 1,2-diol with 5 equiv. of methyl orthoacetate in DCM containing a trace of tosic acid (23 °C, 30 min) furnished **220** in 99% yield.

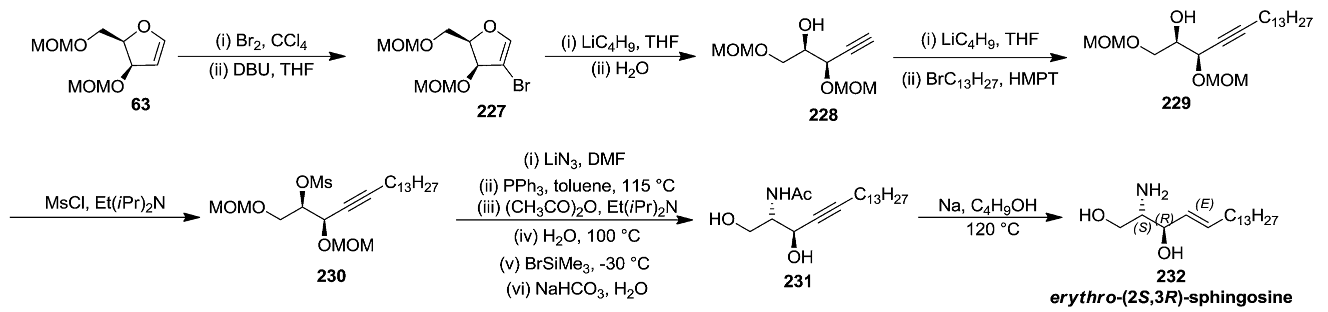
The protected benzoate tosylate **220** was transformed into the *cis*-epoxy aldehyde **221** in 98% yield by the sequential (i) *cis*-epoxidation with K_2CO_3 in MeOH (2 h, 23 °C, 96% yield) (ii) conversion of the cyclic orthoacetate to mono acetate by exposure to wet DCM containing a trace of $pyH^+ TsO^-$ (5 min, 23 °C, 98% yield) to (iii) deacetylation by K_2CO_3 in MeOH (1 h, 23 °C, 99% yield) to form 1,2-glycol and finally (iv) 1,2-glycol cleavage with 1.05 equiv. of $Pb(OAc)_4$ in DCM containing finely powdered sodium carbonate (−45 °C, 5 min). Its chain extension followed by Wittig reaction of resulting dienal **222** with ylide **223** in THF-HMPA gave epoxy methyl ester **224** (methyl ester of the 5*S*,6*R* isomer of leukotriene A).[42] It was converted to 6-*epi*-LTC **225** in two stages: (i) reaction with 2 equiv. of *N*-trifluoroacetylglutathione dimethyl ester and 3 equiv. of Et_3N in a minimum quantity of methanol at 23 °C for 3 h under Ar atmosphere and (ii) deprotection with K_2CO_3 in 4 : 1 dimethyoxyethane-water at 23 °C for 4 h to afford **225**.

Under the identical reaction condition 6-*epi*-LTD **226** was prepared from **224** by using *N*-trifluoroacetylcysteinylglycine methyl ester, and the deprotection step was reported to perform at 23 °C for 18 h (Scheme 38).

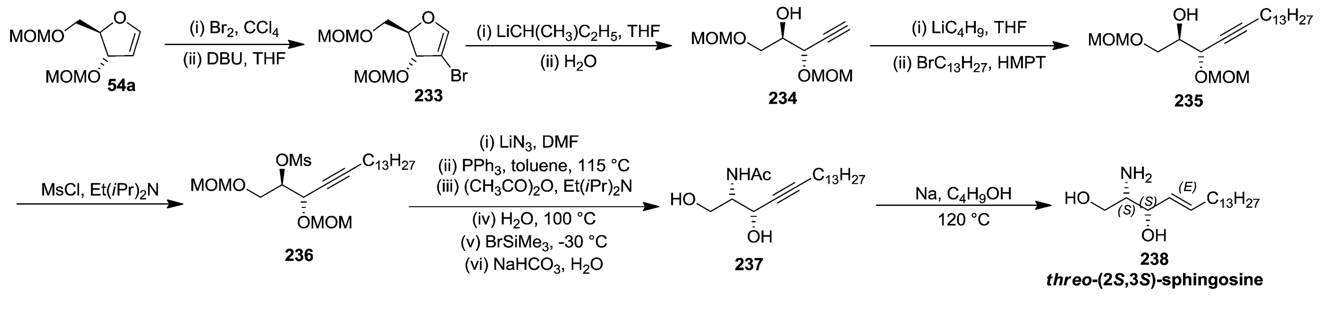
Schlosser and coworkers described the synthesis of *threo*-furanoid glycal **63** (Scheme 11), *erythro* furanoid glycal **54a** (Scheme 10)[20a] and utilized them as key intermediates for synthesis of *erythro*-(2*S*,3*R*)-sphingosine **232** (Scheme 39) and *threo*-(2*S*,3*S*)-sphingosine **238** (Scheme 40).[21]

In 1999, Theodorakis *et al.* described a short, efficient, and enantioselective synthesis of Norrisane side chain from furanoid glycal **139** as key intermediate (Scheme 23).[31] Furanoid glycal **139** was converted into cyclopropanated ester **239** by treatment with ethyl diazoacetate (0.1 M in DCM) and $Rh_2(OAc)_4$ at 25 °C which on treatment with dilute ethanolic solution of sulfuric acid afforded **240**. After its oxidative cleavage in the presence of $NaIO_4$, the resulting aldehyde was methylated to produce **241** in 63% combined yield. Its Swern oxidation produced ketone **242** in 79% yield, which on $MeSO_3H$ mediated cyclization at 0 °C furnished bicycle **243** as a single isomer in 67% yield. Its Baeyer–Villiger oxidation in presence of urea-hydrogen peroxide and trifluoroacetic anhydride yielded **244** in 69% yield (Scheme 41).

In 2001, Chida and co-worker also utilized furanoid glycal **139** as key intermediate for synthesis of (+)-myriocine **262** (Schemes 42 and 43).[37] α-Methyl furanoside **245** was obtained from furanoid glycal **139** in 81% yield by oxymercuration-reduction followed by acid treatment. The primary hydroxyl



Scheme 39



Scheme 40

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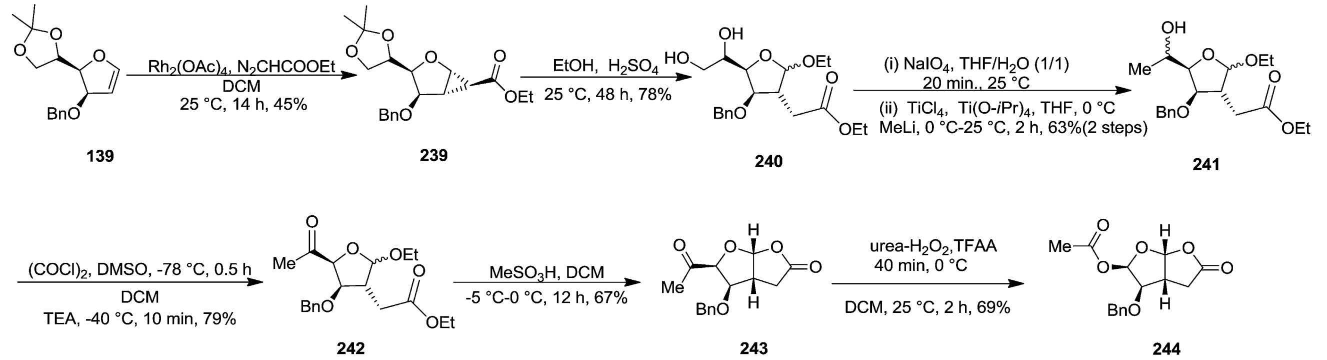
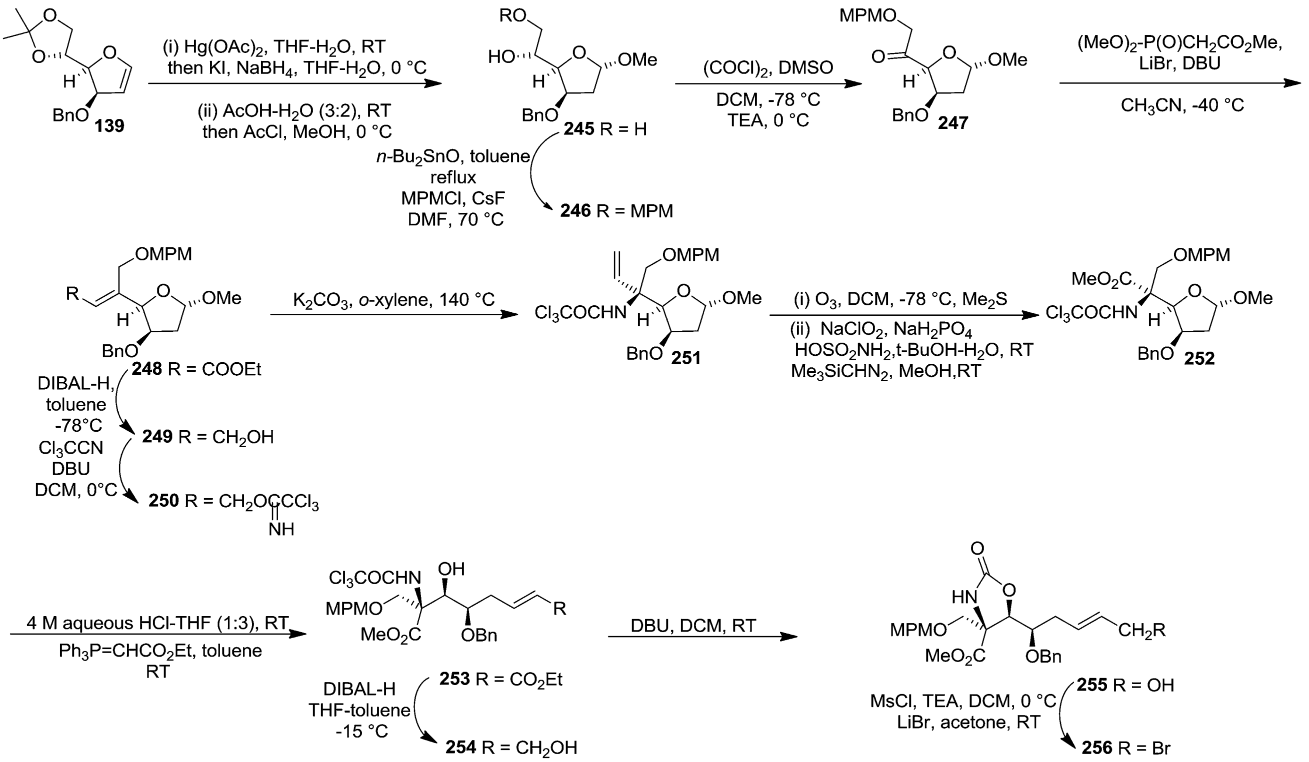


Scheme 41



Scheme 42

group in **245** was selectively *p*-methoxybenzylated to afford **246** (95% yield), which on Swern oxidation generated ketone **247**. Its Horner–Emmons reaction provided an inseparable mixture of (*E*)-alkene **248** and its (*Z*)-isomer (15 : 1) in 90% yield. DIBAL-H reduction of the mixture afforded column purified (*E*)-allyl alcohol **249** and its (*Z*)-isomer in 93% and 6% isolated yields respectively. The allyl alcohol **249** was converted into trichloroacetimidate **250** which, without further purification, was subjected to Overman rearrangement to yield an inseparable mixture of rearranged products **251** and its epimer in a ratio of 7 : 1 in 90% yield from **249**. Ozonolysis of **251** followed by oxidation and esterification in succession afforded **252** (82% yield). Its acid hydrolysis provided an anomeric mixture of lactol which was then treated with $Ph_3P{=}CHCO_2Et$ to give (*E*)-alkene **253** in 71% yield. Its DIBAL-H reduction in THF-toluene at 215 °C afforded allyl alcohol **254** (75% yield), which on treatment with DBU in DCM was transformed into cyclic carbamate **255** in 86% yield. The primary hydroxyl group in **255** was converted into corresponding allyl bromide **256** in 92% yield (Scheme 42).

The hydrophobic part of myriocin, sulfone **258**, was prepared by treatment of 1-bromododecan-6-one **257** with $PhSO_2Na$, followed by ketalization (82% yield) (Scheme 43). Sulfone **258** on treatment with *n*BuLi, and allyl bromide **256** afforded the coupling product **259** in 80% yield. Saponification of **259** and subsequent Birch reduction gave crude carboxylic acid **260**. Removal of the ketal group and carbamate function in **260** followed by conventional acetylation provided **261**. Finally, saponification of **261**

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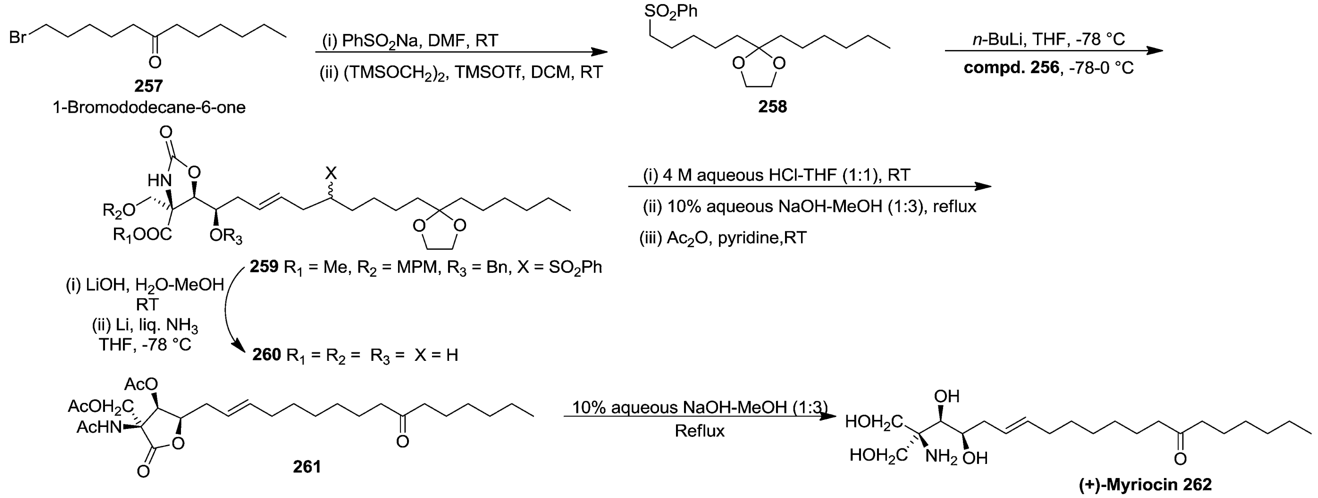


Scheme 43

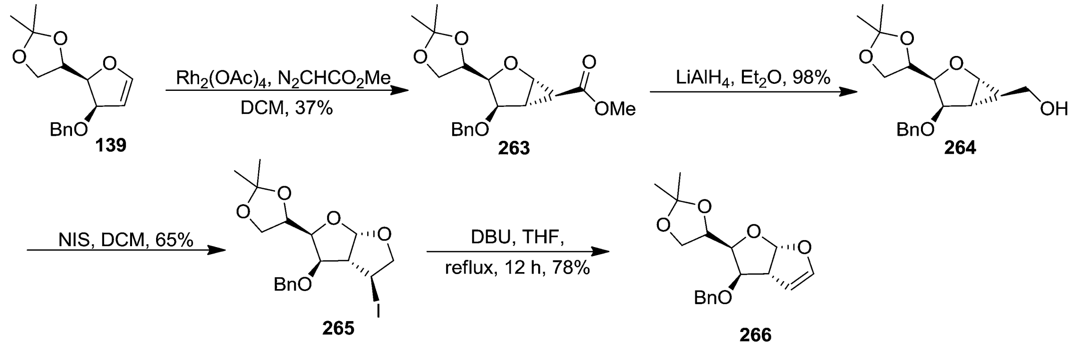
followed by neutralization with weak acidic resin (Amberlite IRC-76, H^+ form) furnished (+)-myriocin **262** in 82% yield.

In 2007, Chandrasekharan and coworker developed a methodology for the construction of fused perhydrofuro[2,3-*b*]pyran/furan by using NIS mediated ring opening and cyclization of 1,2-cyclopropanated sugar derivatives, derived from pyranoid and furanoid glycals. They successfully applied this methodology to the synthesis of fused perhydrofuro[2,3-*b*]pyrano/furano-γ-butyrolactone derivatives using sugar derived 1,2-cyclopropane carboxylic acids.[43]

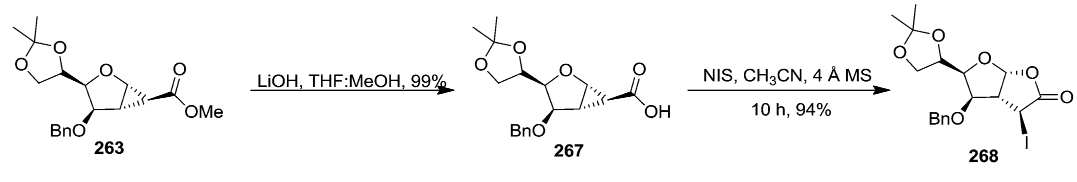
The furanoid glycal **139** on treatment with methyl diazoacetate in the presence of $Rh_2(OAc)_4$ gave the cyclopropanated ester **263** as a major product, which on LAH reduction delivered alcohol **264** in 98% yield. It was subjected to NIS mediated ring opening and cyclization reaction to furnish perhydrofuro[2,3-*b*]furan derivative **265** in 65% yield as a mixture of diastereomers (9 : 1). The mixture was subjected to dehydrohalogenation with DBU (THF, reflux, 12 h) to obtain the corresponding furofuryl glycal **266** in 78% yield (Scheme 44).

The hydrolysis of the 1,2-cyclopropane carboxylate **263** under the basic medium produced 1,2-cyclopropane carboxylic acid **267** (Scheme 45). Its cyclopropane ring opening with NIS in presence of CH_3CN and 4 Å MS for 10 h furnished the corresponding 3-iodoperhydrofuro[2,3-*b*]furano-γ-butyrolactone derivative **268** in excellent yield (83%) (Scheme 45).

In 2007, Correia and co-workers achieved the synthesis of (−)-isoaltholactone **277** in seven steps with an overall yield of ~25% from L-glutamic acid **269** derived furanoid glycal **270** (ref.



Scheme 44



Scheme 45

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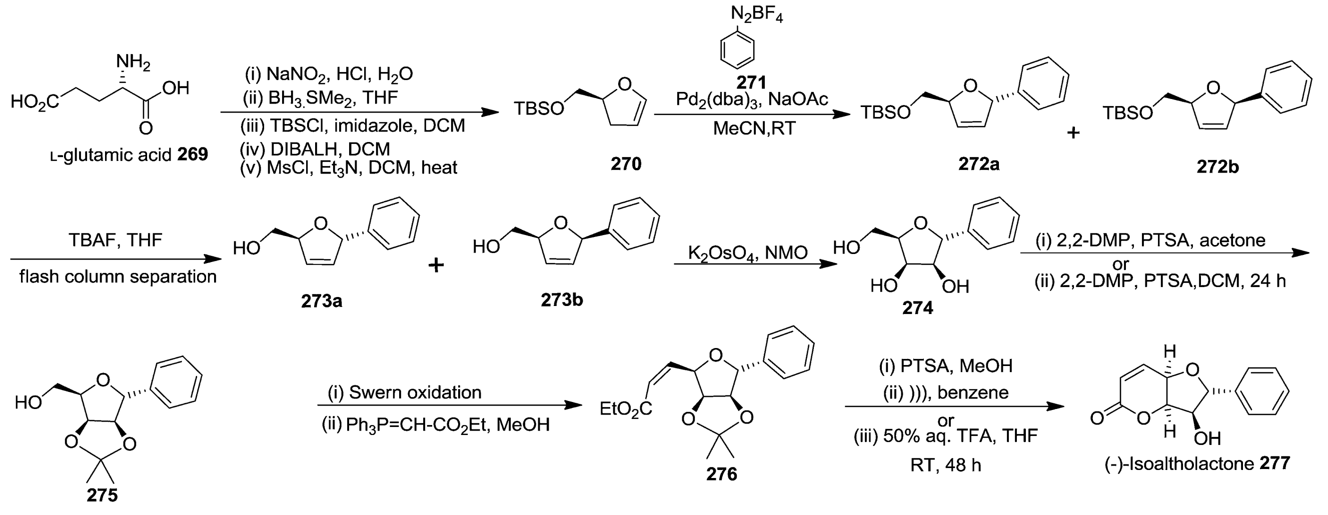
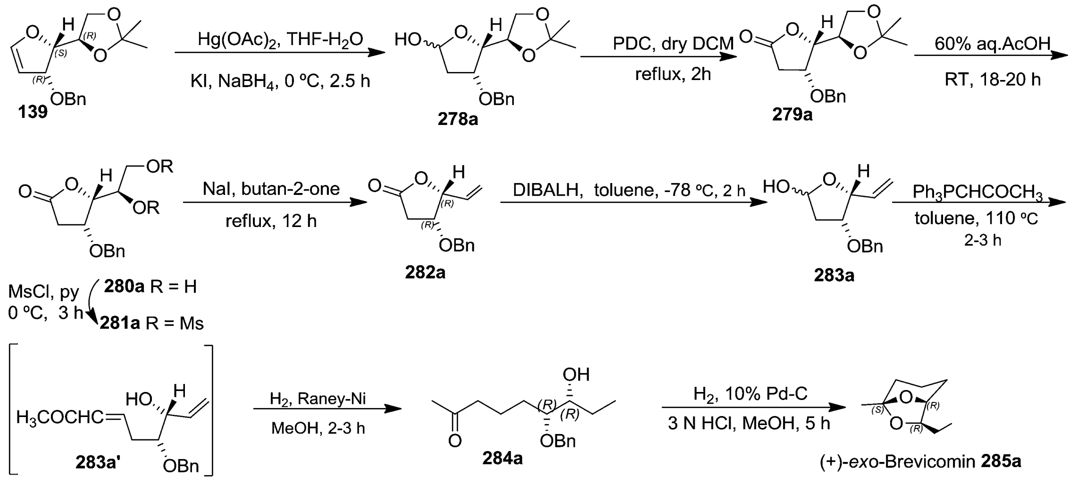
44) by utilizing Heck–Matsuda arylation with benzenediazonium tetrafluoroborates as the key step.[45] After performing several trial and error experiments, they achieved the best condition for Heck–Matsuda arylation of enolether **270** with benzenediazonium tetrafluoroborates **271** in the presence of 4 mol% of $Pd_2(dba)_3$, to afford the phenyldihydrofurans **272a** and **272b** in 90% yield as a 94 : 06 inseparable diasteromeric mixture. Though the diastereomeric mixture was inseparable by column chromatography, the desilylated Heck adducts were separated. The silyl ether deprotection of **272** followed by column purification resulted **273a** and **273b**. Treatment of **273a** with potassium osmate and *N*-methylmorpholine N-oxide (NMO) afforded the triol **274** which, without further purification, was treated with 2,2-dimethoxypropane and PTSA to give acetonide **275** in good yields (Scheme 46). Swern oxidation of free hydroxyl group of **275** gave an unstable aldehyde which was immediately subjected to a Wittig olefination with ethoxycarbonylmethylene phosphorane in methanol to furnish the *cis*-enoate **276** in 75% yield (over 2 steps). It was then treated with catalytic PTSA in methanol followed by sonication to obtain (−)-isoaltholactone **277** in 70% yield (2 steps). However, when *cis*-enoate **276** was treated with an aqueous solution of trifluoroacetic acid for 48 h at room temperature, the (−)-isoaltholactone **277** was obtained in 80% yield (Scheme 46).

After reporting an efficient protocol for the synthesis of stereochemically pure four different furanoid glycals (**162a–c, 139**) (Fig. 3) from our laboratory, in the year 2011, we were further interested to demonstrate the synthetic utility of these furanoid glycals. In this endeavour, we identified and synthesized four aggregation pheromones brevicomins (**285a–d**), styryllactones (+)-cardiobutanolide **290a**, (−)-cardiobutanolide **290b** and (+)-goniofufurone **295a** from the above mentioned furanoid glycals (**162a–c, 139**).[2h]

The total synthesis of (+)-*exo*-brevicomin **285a** was initiated from furanoid glycal **139** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-D-arabino-hex-1-enitol) (Scheme 47), which was converted into **278a** by oxymercuration–demercuration sequence in 98% yield. The anomeric OH was oxidized with



Scheme 46



Scheme 47

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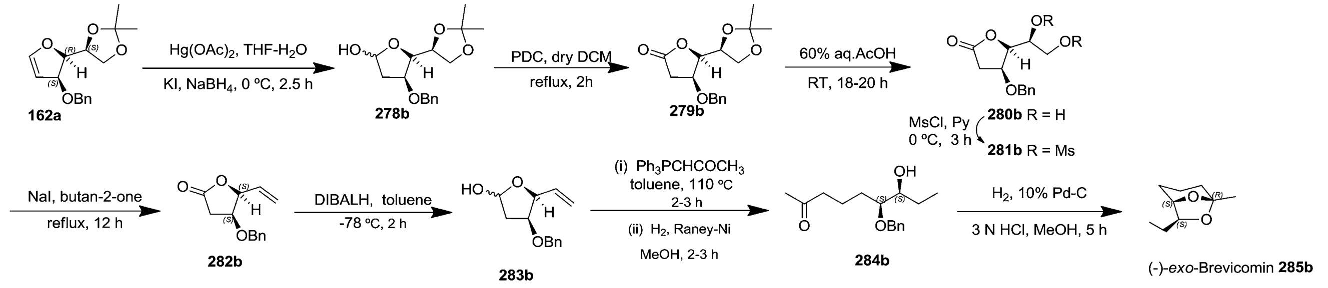
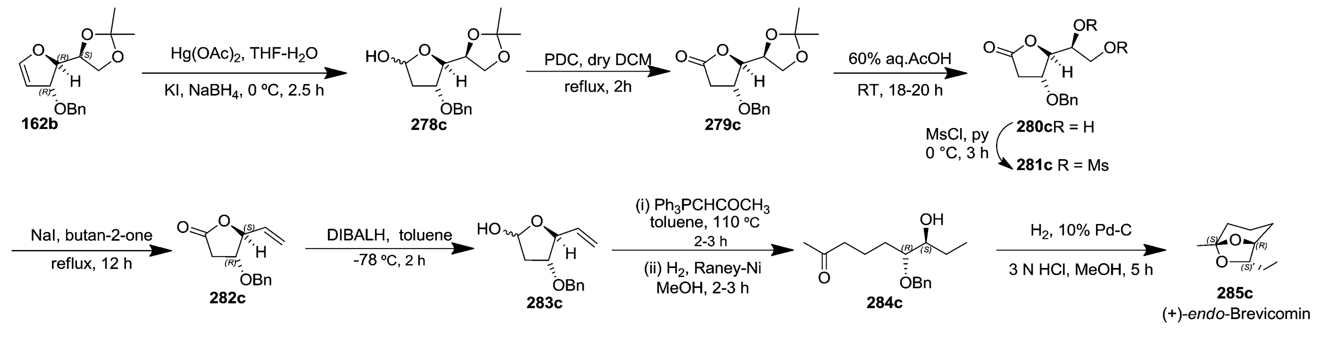


Scheme 48

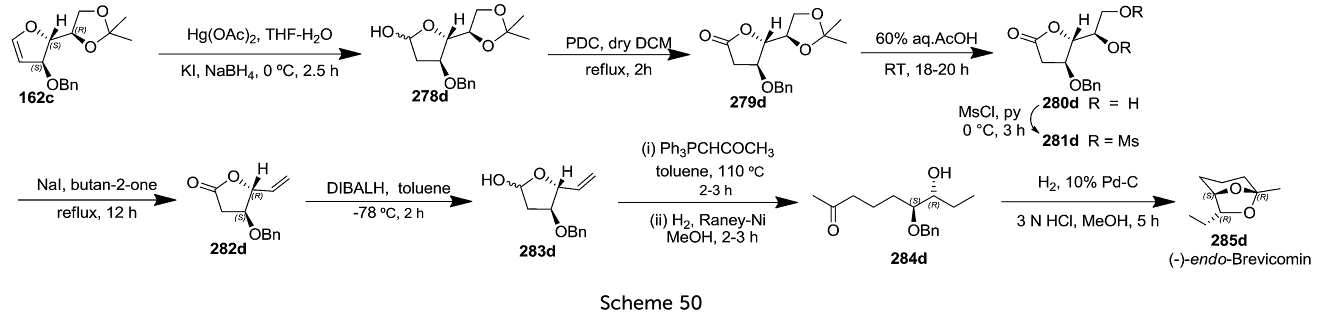
PDC in dry DCM at refluxing temperature for 2 h to obtain lactone **279a** as a white solid in 75% yield. Deprotection of the acetonide in **279a** was carried out with 60% aqueous AcOH at room temperature for 18–20 h to give diol **280a** as a white solid, which was without further purification, mesylated with MsCl in pyridine at 0 °C for 3 h to afford dimesyl derivative **281a**. The reductive elimination of diester **281a** with NaI in butan-2-one at reflux temperature for 12 h yielded vinylbutyrolactone derivative **282a** in 71% yield for three steps. Its reduction with DIBALH at −78 °C in dry toluene yielded lactol **283a** in 86% yield. Its Wittig olefination with $Ph_3PCHCOCH_3$ in dry toluene followed by RANEY® hydrogenation of the resulting product **283a'** with two double bonds afforded column purified ketone **284a** in 52% yield in two steps. Finally, the simultaneous hydrogenolysis of OBn in **284a** in presence of Pd/C in MeOH and intramolecular acetalization with a trace of 3 N HCl delivered the target (+)-*exo*-brevicomin **285a** in 44% yield (Scheme 47).

After having completed the total synthesis of (+)-*exo*-brevicomin **285a** from furanoid glycal **139**, the similar reaction sequence was successfully followed for the synthesis of (−)-*exo*-brevicomin **285b** from **162a** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-L-arabino-hex-1-enitol) (Scheme 48), (+)-*endo*-brevicomin **285c** from **162b** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-L-*ribo*-hex-1-enitol) (Scheme 49) and (−)-*endo*-brevicomin **285d** from **162c** (1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-3-*O*-benzyl-D-*ribo*-hex-1-enitol) (Scheme 50).

The key intermediates **282a** and **282b** (Schemes 47 and 48) were utilized for the synthesis of styryllactones (+)-cardiobutanolide **290a**, (−)-cardiobutanolide **290b**. The olefin cross metathesis reaction between **282a** and (*S*)-1-phenyl-2-propene-1-ol with Grubb's IInd generation catalyst (2.8 mol%) in refluxing DCM furnished allylic alcohol **286a** in 74% yield. It was silylated with TBSCl in dry DCM at 0 °C to afford silyl ether **287a** in 93% yield. Its asymmetric dihydroxylation with AD-mix-β in 1 : 1 *t*BuOH : H_2O afforded **288a** in 67% yield which on silyl ether deprotection with amberlyst 15 resin in dry acetonitrile produced **289a** in 94% yield. Finally, its *O*-benzyl deprotection by $Pd(OH)_2$ catalyzed hydrogenolysis in dry MeOH furnished the



Scheme 49



Scheme 50

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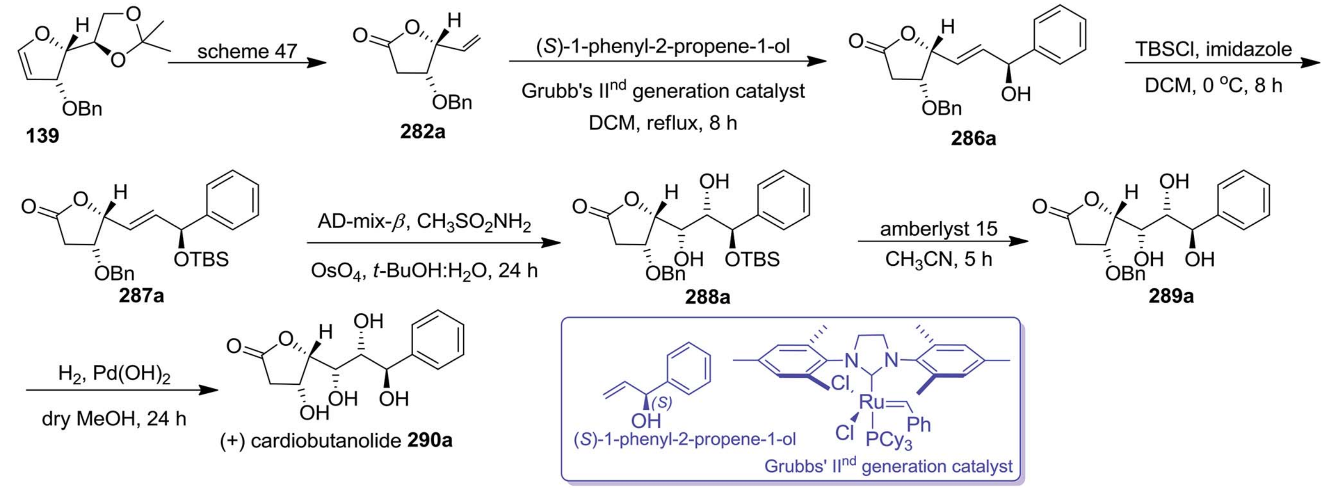
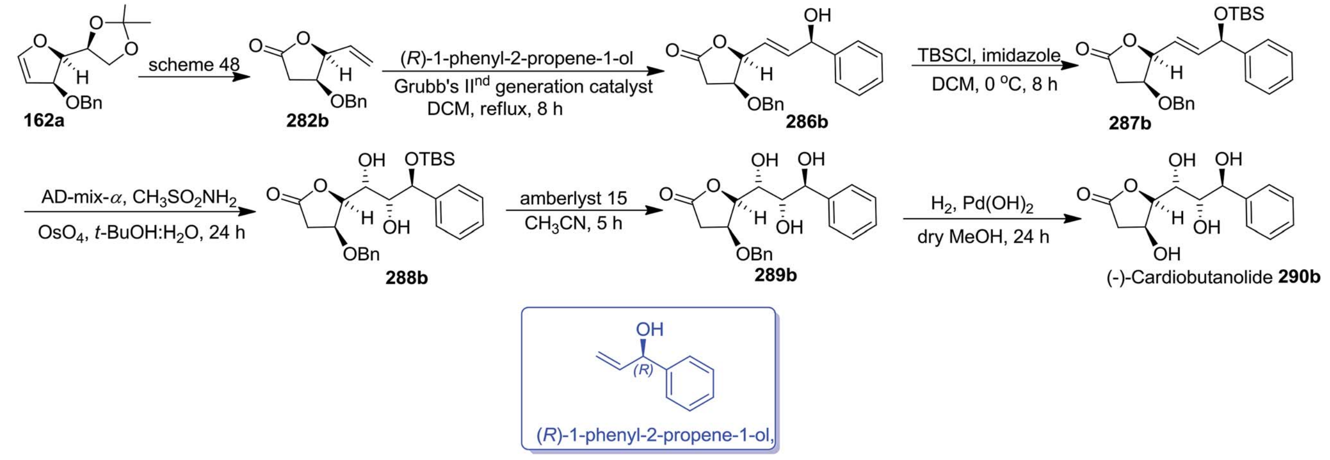
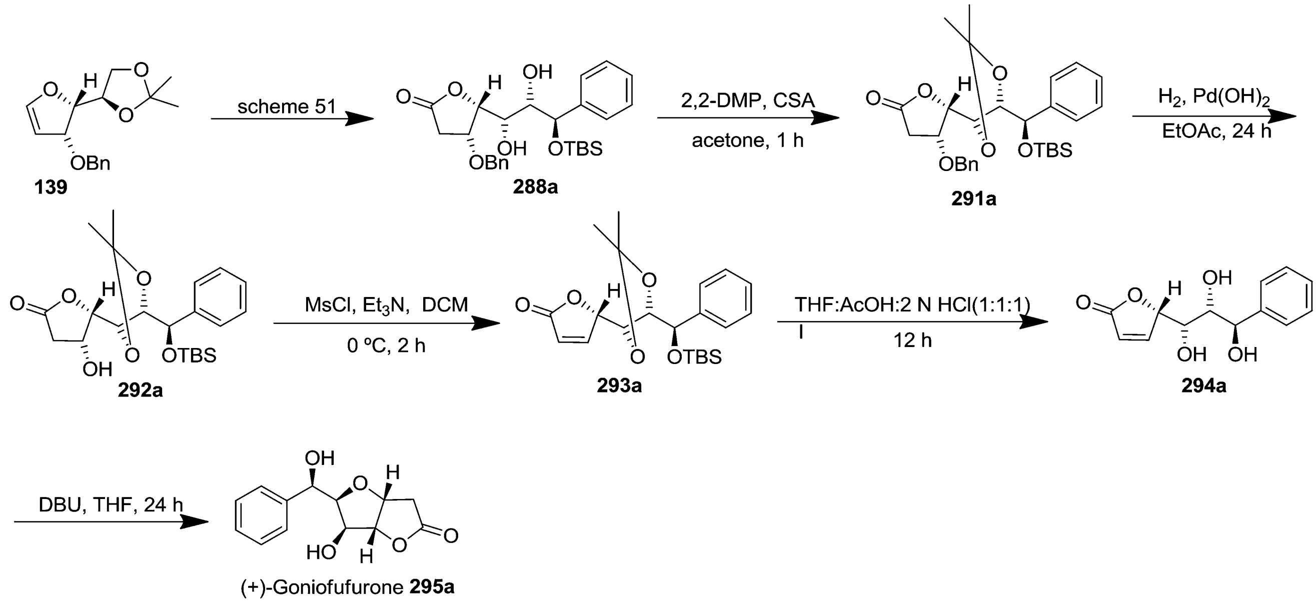


Scheme 51



Scheme 52



Scheme 53

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desired natural product (+)-cardiobutanolide **290a** in 67% yield (Scheme 51).

Similarly, the (−)-cardiobutanolide **290b** was synthesized from **162a**, an optical antipode of **139** by adopting the reaction sequence similar to that employed for the synthesis of its enantiomer **290a.** The olefin cross metathesis reaction between compound **282b** derived from **162a** (Scheme 48) and (*R*)-1-phenyl-2-propene-1-ol with Grubb's IInd generation catalyst (2.8 mol%) furnished allylic alcohol **286b** in 74% yield. Its silylated derivative **287b** on asymmetric dihydroxylation with AD-mix-α in 1 : 1 *t*BuOH : H$_2$O afforded **288b**. After having **288b** in hand, the remaining two synthetic steps similar to that employed for the synthesis of (+)-cardiobutanolide **290a** (*vide supra*) were followed to complete the synthesis of (−)-cardiobutanolide **290b** (Scheme 52).

The acetonide protection of two free OH in **288a** (obtained from furanoid glycal **139**, Scheme 51) afforded globally OH protected derivative **291a** in 83% yield. Its hydrogenolysis in the presence of Pd(OH)$_2$ in dry EtOAc gave *O*-benzyl deprotected derivative **292a** in 87% yield which on mesylation with MsCl-Et$_3$N at 0 °C in dry DCM for 2 h followed by elimination of MsOH under basic condition furnished the α,β-unsaturated lactone **293a** in 92% yield. Its treatment with THF/AcOH/2 N HCl (1 : 1 : 1) at room temperature delivered the triol **294a** in 56% yield. Finally, it was subjected to DBU catalyzed bicyclic ring formation by the participation of its 6-OH to furnish the title natural product (+)-goniofufurone **295a** as a white solid in 64% yield (Scheme 53).

4. Some reactions of furanoid glycals

4.1. Peroxidation, osmylation, mercuration and bromination

After describing the synthesis of furanoid glycal **24**, **26** and **30** (Scheme 4),[16a] Bischofberger *et al.* in 1979 discussed some important reactions on furanoid glycals (1,4-anhydro-2-deoxy-3-*O*-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)-5,6-*O*-isopropylidene-D-arabino-hex-1-enitol **24** and 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-D-arabino-hex-1-enitol **26**.[46] Oxidation of **26** with *m*-CPBA in absolute ethanol gave hex-2-enofuranosides **296** (26% yield), and also two ethyl furanosides **297** (7% yield) and **298** (15% yield) by *trans*-ring opening of 1,2-epoxide intermediates. Under the identical reaction condition, furanoid glycal **24** afforded β-D-glucoside **299** as major product in 62% yield. Here the oxidant preferentially attacked from the α-side to form 1,2-epoxide intermediate due to the β-*C*-3 bulky group (Scheme 54).

They further described that osmylation of **26** with OsO$_4$ in pyridine, followed by cleavage of osmate ester and acetylation gave column purified β-D- and α-D-glucofuranoses, **300** (30% yield) and **301** (17% yield), respectively, indicating that attack by the oxidant took place mainly from the α-face. Similarly, osmylation reaction of the glycal **24**, followed the same reaction sequence to form isolated anomeric gluco-furanoses **302** (14% yield) and **303** (26% yield) and a mixture of manno-furanoses **304** (gluco : manno, 7 : 1).

Methoxymercuration of **26** with Hg(OAc)$_2$ in dry methanol, followed by demercuration with NaBH$_4$ and acetylation yielded 2-deoxy derivatives **305** and **306** respectively. Methoxymercuration-demercuration of **24** furnished only one product **307** having the anomeric methoxy group in β-configuration.

Ethoxybromination of **26** with *N*-bromosuccinimide (NBS) in acetonitrile–ethanol, followed by acetylation produced mainly the ethyl-β-D-glucoside **308** (28% yield), with the α-D-glucoside **309** (3% yield) with other minor side products (6% yield). Debromination of **308** and **309** with *n*Bu$_3$SnH in the presence of AIBN in benzene afforded 2-deoxy derivatives **310** and **311** respectively. Ethoxybromination of **24** furnished a mixture of ethyl-2-bromo-2-deoxy-furanosides **312** (19% yield) and an anomeric mixture of a 2-bromo-2-deoxy-furanose **313.** Acetylation of **313** gave separable anomeric acetates having β-D-gluco configuration **314** and α-D-gluco configuration **315** respectively, whose debromination formed **316** and **317** respectively and debromination of **312** yielded **318** (Scheme 54).

In 1987, Dax *et al.* demonstrated the reaction of acetyl hypofluorite (CH$_3$CO$_2$F) with pyranoid and furanoid glycals and they observed that more stereospecific reactions took place with furanoid glycals. Treatment of 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-D-arabino-hex-1-enitol[16,19] **26** or 1,4-anhydro-2-deoxy-5-*O*-methoxymethyl-D-*erythro*-pent-1-enitol[4] **45** with gaseous acetyl hypofluorite in DCM-hexane at room temperature gave a complex mixture of compounds. Among them 1-*O*-acetyl-2-deoxy-2-fluoro-5,6-*O*-isopropylidene-β-D-mannofuranose **319** was obtained from **26** in 47% yield and 1-*O*-acetyl-2-deoxy-2-fluoro-5-*O*-methoxymethyl-α-D-ribofuranose **322** from **45** in 30% yield as major products (Scheme 55).[47]

On the other hand, while 3-*O*-benzyl derivative **139** (ref. 31 and 35–37) (derived from glycal **26**), on treatment with gaseous acetyl hypofluorite led to the formation of only 1-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-5,6-*O*-isopropylidene-α-D-glucofuranose **320**, and **323** from the glycal **45**, under the identical reaction conditions formed two fluorinated products *viz.* 1-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-5-*O*-methoxymethyl-β-D-arabinofuranose **324** and its analogue **325.** Compounds **320** and **324** were debenzylated to afford 1-*O*-acetyl-2-deoxy-2-fluoro-5,6-*O*-isopropylidene-α-D-glucofuranose **321** and 1-*O*-acetyl-2-deoxy-2-fluoro-5-*O*-methoxymethyl-β-D-arabinofuranose **326**, respectively (Scheme 55). They concluded from this study that free 3-OH of **26** and **45** induced the exclusive *syn* addition of acetyl hypofluorite across the double bond to afford their respective compounds **319** and **322**, whereas benzyloxy derivatives **139** and **323** caused attack from the less-hindered opposite face of the double bond to afford **320** and **324** respectively.

4.2. Cycloaddition reaction

4.2.1. Diels–Alder reaction.

In 1987, Leblanc *et al.* discussed a new and efficient method for the preparation of 2-deoxy-2-aminoglycosides in high yields by stereoselective [4+2] cycloaddition reaction of dibenzyl azodicarboxylate (BnO$_2$C–N=N–CO$_2$Bn) on the appropriate glycals (Scheme 56, Table 7).[48] Irradiation of glycals (**327**, **66f**, **214** and **336**) with dibenzyl azodicarboxylate (DBAD) in cyclohexane at 350 nm for 18 h gave single [4+2] cycloadduct (**328**, **331**, **333** and **337**) respectively. Treatment of these cyclo adducts with a catalytic amount of

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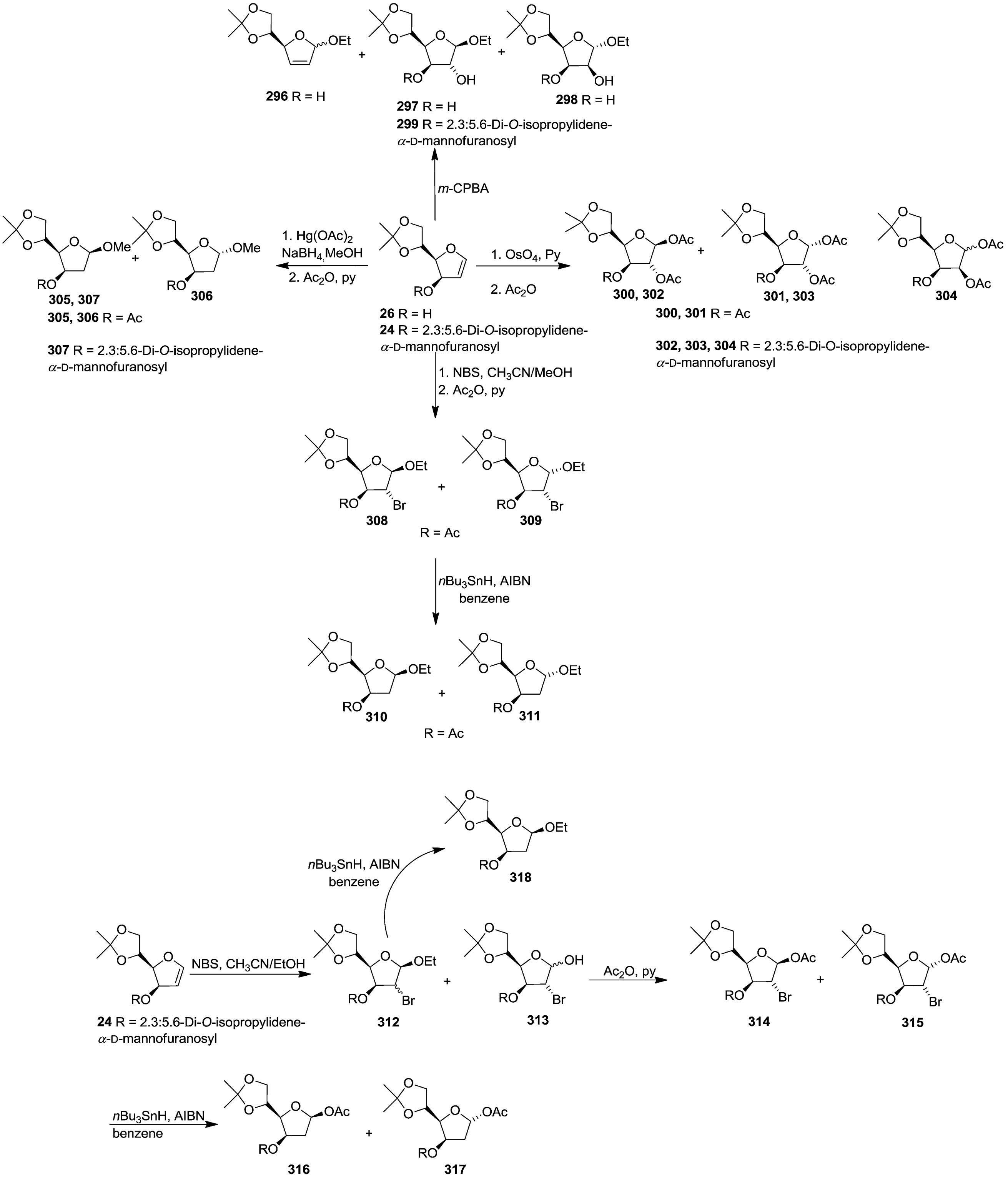

Scheme 54

PTSA in MeOH led to opening at C-1 with inversion of stereochemistry to afford the corresponding methyl glycosides (**329**, **332**, **334**, **338**) in quantitative yield. Hydrogenolysis of the protected hydrazines gave the 2-amino glycosides (**330**, **335**, **339**) in high yields (Scheme 56).

Since amino sugars present in natural products are usually in the pyranoside form, that's why they also showed the conversion of furanoside **342** into pyranoside **343** (Scheme 57).[48] Later they reported similar reactions with several pyranoid glycals to obtain 2-amino pyranosides.[49]

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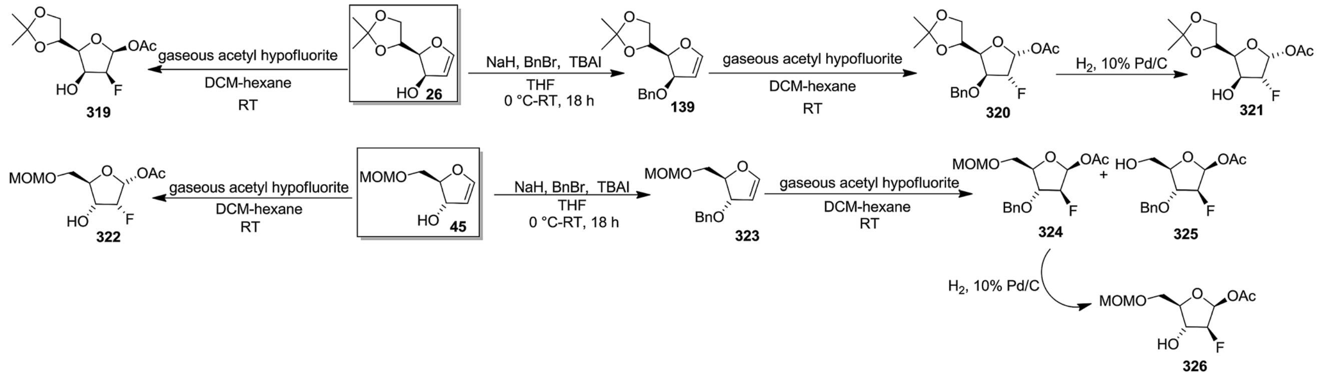
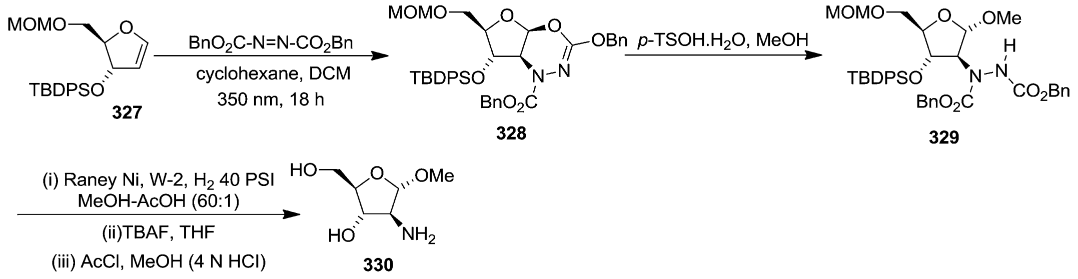
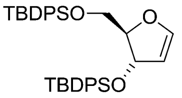
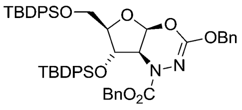
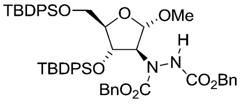
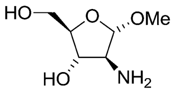
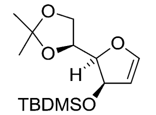
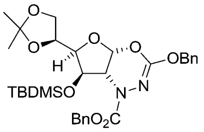
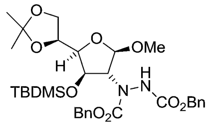
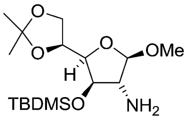
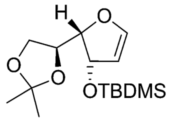
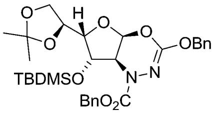
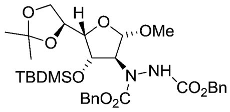
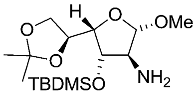


Scheme 55

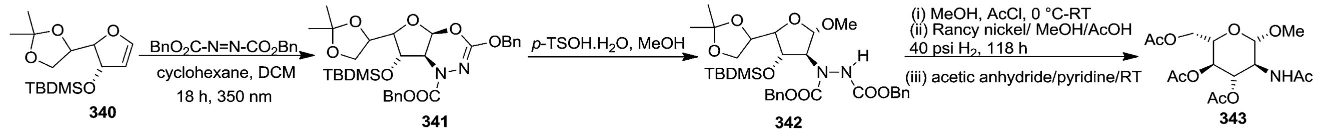


Scheme 56

Table 7 Preparation of 2-deoxy-2-aminoglycosides

Glycal	[4+2]adduct	Glycoside	Free amine
 **66f**	 **331(70%)**	 **332 (88%)**	 **330^a(73%)**
 **214**	 **333 (13%)**	 **334 (88%)**	 **335 (86%)**
 **336**	 **337 (80%)**	 **338 (80%)**	 **339 (98%)**

^{a} The hydrogenolysis was performed on the free diol obtained by desilylation of compound **332** (n-Bu_4NF 10 equiv, AcOH 3 equiv, THF, 90%).



Scheme 57

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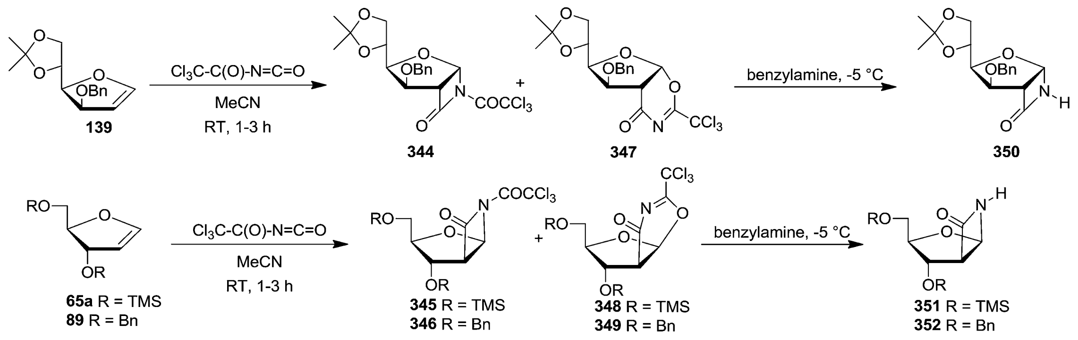
In 1993, Chmielewski *et al.* showed [2+2] cycloaddition of trichloroacetyl isocyanate to furanoid glycals. Here, the preferential attacked of the reagent to the substrate was governed by the stereochemistry of the C-3 substituent. They selected furanoid glycals **139**, **65a** and **89** which on treatment with trichloroacetyl isocyanate in acetonitrile at room temperature afforded a mixture of [2+2] cycloadducts (**344–346**) and [4+2] cycloadducts (**347–349**) in a 1 : 1 ratio in each case. Deprotection of the nitrogen atom in (**344–346**) produced stable bicyclic β-lactams (**350–352**). The α-D-gluco configuration for **350** and β-D-arabino configuration for **351** and **352** confirmed cycloaddition proceeded exclusively *anti* to the C-3 substituent (Scheme 58).[50]

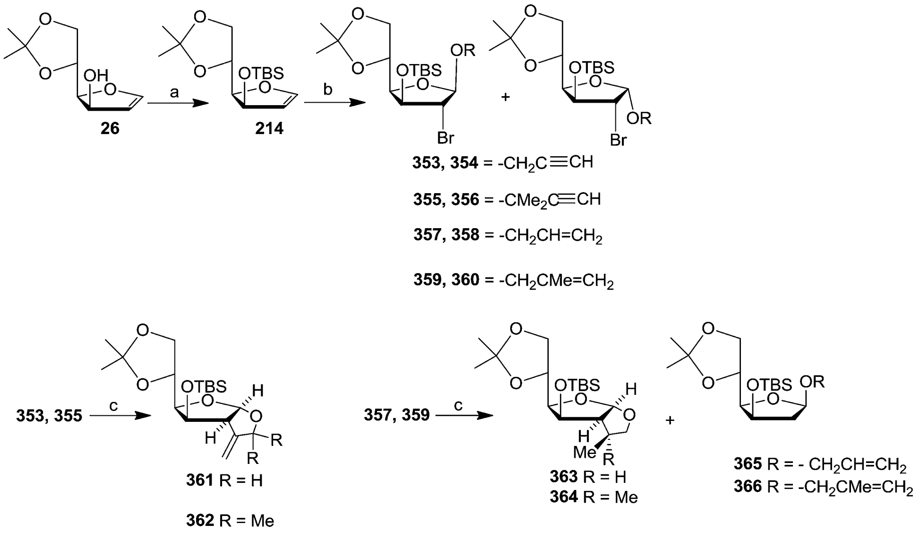
4.2.2. Radical cyclization. Sharma and coworkers described a protocol involving intramolecular radical cyclization of furanoid glycal derived α-halogeno acetal derivatives.[36] Furanoid glycal **26** was silylated with TBSCl or TBDMSCl in the presence of imidazole in DMF yielded **214** in 83%. Treatment of **214** with NBS in the presence of respective propargylic and allylic alcohols *viz.* 2-propyn-1-ol, 2-methyl-3-butyn-2-ol, 2-propen-1-ol, and 2-methyl-2-propen-1-ol resulted in stereoselective formation of 1,2-*trans*-β-D-glycosides, **353**, **355**, **357** and **359** respectively as major products and **354**, **356**, **358** and **360** as minor products. The crucial regio- and stereo-selective intramolecular C–C bond formation on **353**, **355**, **357** and **359** was efficiently achieved by treating each with a catalytic amount of $n\text{Bu}_3\text{SnCl}$ and AIBN in the presence of NaBH_3CN in refluxing *t*BuOH to afford the respective *cis-fused* bicyclic acetals (**361–364**) in 30–72% yield by a preferred *5-exo* mode of cyclization. During the radical cyclisations, the propargylic glycosides **353** and **355** gave **361** and **362** as exclusive products, while the allylic glycosides **357** and **359** gave the expected cyclized products **363** and **364** along with the 2-deoxy compounds **365** and **366** respectively (Scheme 59).

4.3. Wittig rearrangement

Gesson *et al.* studied[51] the [2,3]-Wittig rearrangement of **369**, **375**, **379** derived from furanoid glycals **26**, **367**, **53b** which were easily derived from D-mannose, L-gulonic-γ-lactone and D-ribonic-γ-lactone respectively.[19,20a] The C-3 free hydroxyl group of these furanoid glycals (**26**, **367**, **53b**) was alkylated with propargyl bromide in the presence of NaH in THF to form **368**, **374**, **378** which on treatment with *n*BuLi (1.1 eq.) in THF at



Scheme 58



Scheme 59 Reagents and conditions: (a) TBSCl, imidazole, DMF, 83%; (b) NBS, 10 equiv. 2-propyn-1-ol (for **353**, **354**), 2-methyl-3-butyn-2-ol (for **355**, **356**), 2-propen-1-ol (for **357**, **358**), and 2-methyl-2-propen-1-ol (for **359**, **360**) respectively; (c) $n\text{Bu}_3\text{SnCl}$, AIBN, NaBH_3CN, *t*BuOH, reflux.

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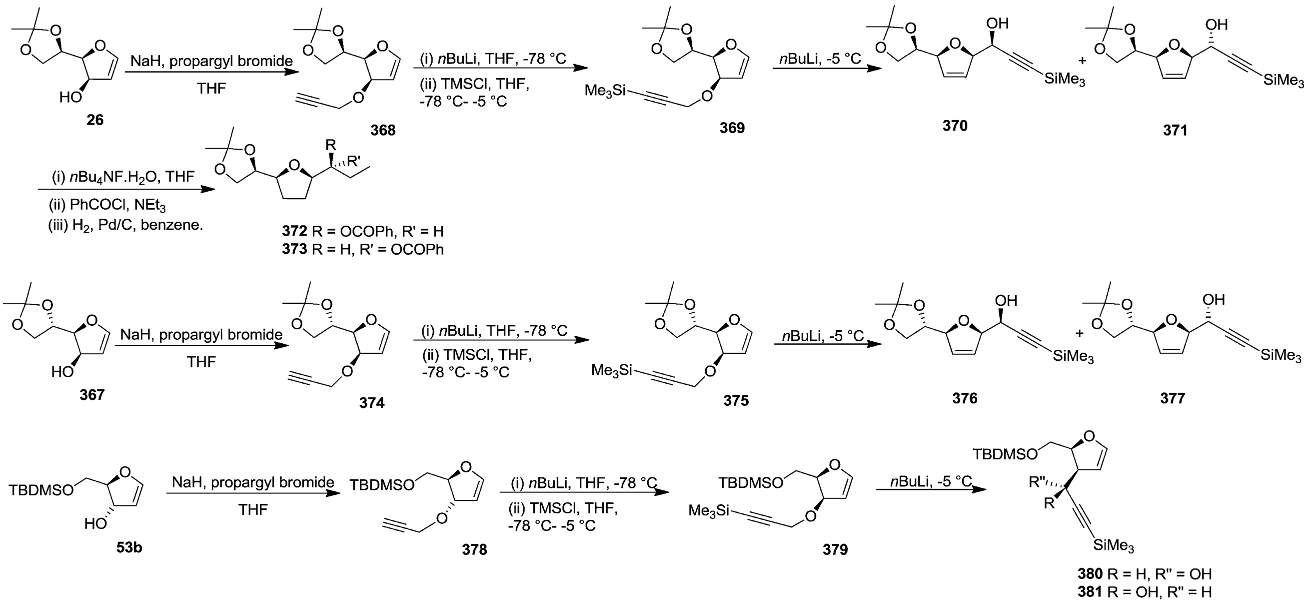
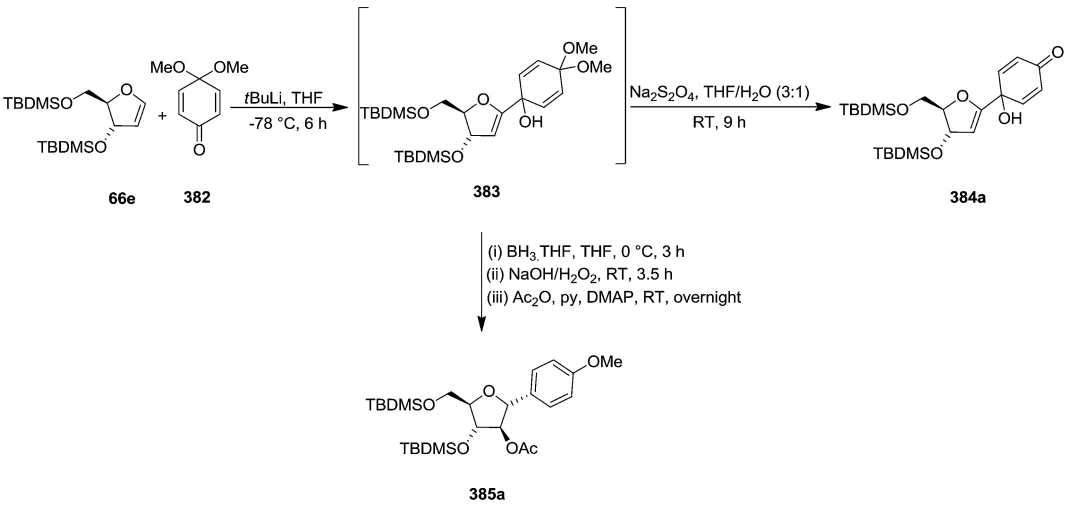
−78 °C followed by addition of TMSCl (1.1 eq., −78 °C to −5 °C) afforded **369**, **375**, **379** respectively. These trimethylsilylpropargyl ethers of furanoid glycals **369**, **375**, **379** were used in a one-pot [2,3]-Wittig rearrangement by addition of a further 1.1 eq. of *n*BuLi at −5 °C. The glycal derivative **369**, under the identical reaction condition produced easily separable mixture of **370** and **371** in a 7 : 3 ratio with 61% overall isolated yield from **26**. The formation of the major isomer with *erythro* configuration was confirmed by converting **370** and **371** into **372** and **373** respectively through sequence of reactions involving desilylation, benzoylation followed by hydrogenation. The rearrangement of **375** afforded **376** and **377** with higher selectivity in 9 : 1 ratio but in lower overall yield (40%) from **367**. Under the same conditions, **379** gave an inseparable mixture of **380** and **381** in a 2 : 1 ratio (Scheme 60).

4.4. Reverse polarity strategy

Parker and Su, utilized "Reverse Polarity" strategy for the synthesis of C-aryl furanosides from furanoid glycals.[52] They started with furanoid glycal **66e** for the synthesis of C-1 aryl arabino-furanosides (**385a–c**). Lithiation of **66e** with *t*BuLi and addition of the resulting reagent to quinone ketal **382** gave quinol ketal **383**, which without further purification was treated with sodium dithionite to afford C-aryl glycal. But instead of that, quinol **384a**, the hydrolysis product, was obtained in 53% yield. However, the reductive aromatization and anti-Markovnikov hydration was made possible by treating crude **383** with borane-THF followed by stirring with NaOH/H_2O_2 and acylation to obtain 2′-acetate **385a** in an 40% overall yield from glycal **66e** (Scheme 61).



Scheme 60



Scheme 61

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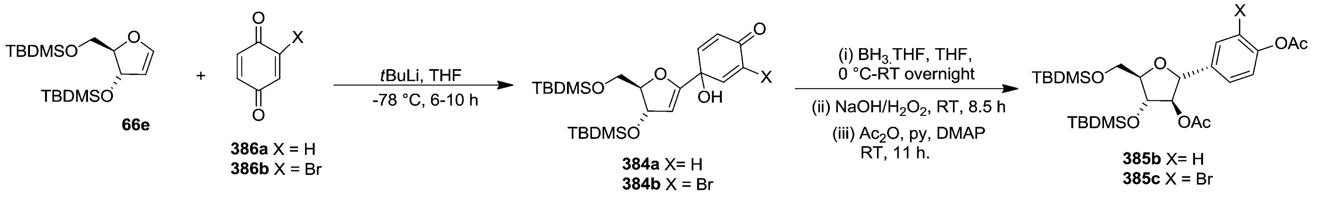


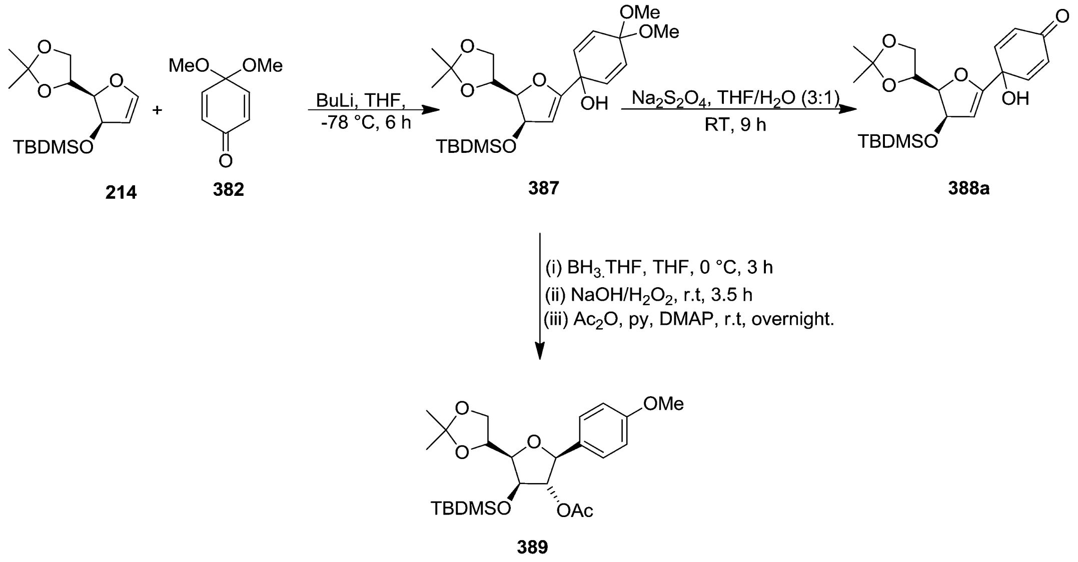
Scheme 62

By utilizing same reaction sequence, they synthesized C-aryl furanosides **385b** and **385c** in good yields starting from furanoid glycal **66e**, *via* intermediates (**384a–b**) (Scheme 62).

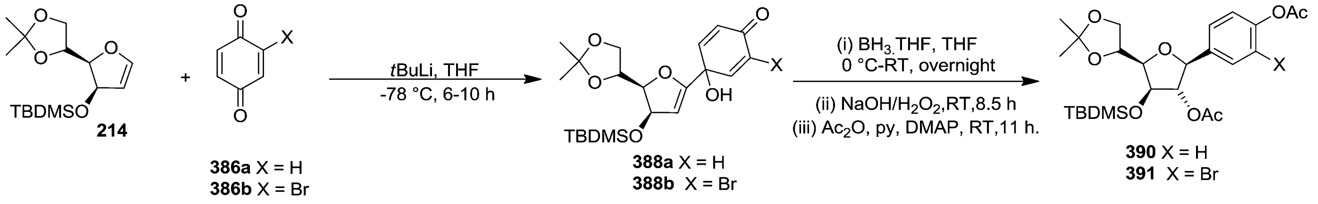
They have also reported the synthesis of C-1 aryl glucofuranosides **389, 390, 391** in good yields from furanoid glycal **214**, by utilizing same reaction sequence (Schemes 63 and 64).

4.5. Metal mediated amination

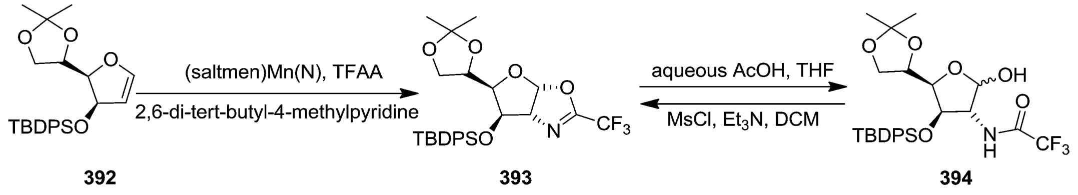
Carrier and group have synthesized stereoselectively 2-amino saccharides through metal-mediated amination of glycal substrates. They studied this reaction on differently protected pyranoid and furanoid glycals by utilizing (saltmen)Mn(N) and TFAA to transfer CF_3CON unit to electron rich silyl enol ethers. The oxazoline **393** was isolated on treatment of furanoid glycal



Scheme 63



Scheme 64



Scheme 65

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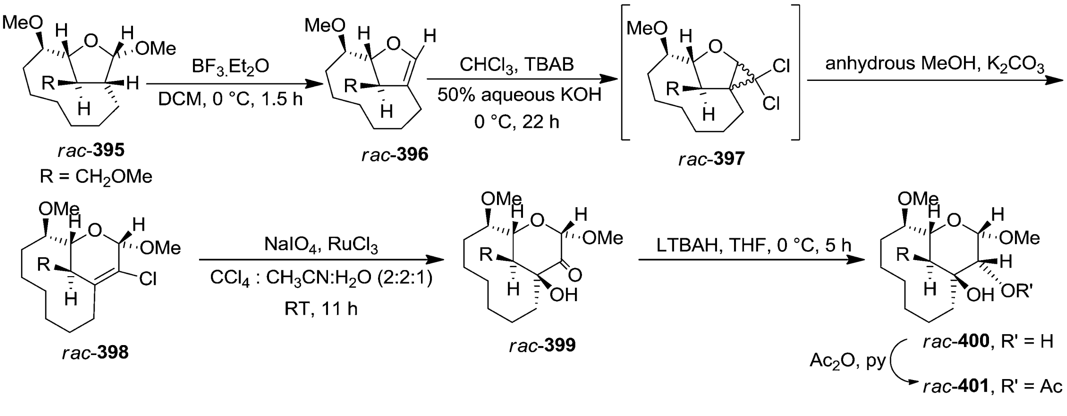

Scheme 66

392 with (saltmen)Mn(N) and TFAA, which, under mild acidic conditions furnished the N-protected amino alcohol **394**. Its structure was confirmed by converting it back to the oxazoline **393** upon treatment with MsCl, Et_3N, DCM (Scheme 65).[53]

4.6. Ring expansion

In 2000 Totchtermann *et al.* reported the formation of heptano-bridged pyranosides by ring enlargement of the glycal *rac*-**396**,[54] which was prepared from heptano bridge methyl furanoside *rac*-**395** by treatment with $BF_3 \cdot Et_2O$ in DCM in 95% isolated yield. Treatment of *rac*-**396** with 50% aq. KOH in the presence of catalytic amounts of nBu$_4$NBr in $CHCl_3$ for 22 h at 0 °C afforded dichloro intermediate derivative *rac*-**397**, which was without further purification refluxed in anhydrous methanol with a large excess of K_2CO_3 to give chloro-2*H*-pyran *rac*-**398** in 60% isolated yield over two steps. Oxidation of *rac*-**398** with RuO_4 yielded *rac*-**399** in 67%. The stereoselective reduction of *rac*-**399** with LTBAH provided the methyl pyranoside *rac*-**400** in 71% isolated yield, which was transformed into corresponding acetate *rac*-**401** in 90% yield (Scheme 66).

5. Synthesis of *C*-nucleosides

The synthesis of nucleoside analogues having modified sugar and/or nucleobases moieties has received much attention because of their general biological activities[55] and potential use as antiviral[56,57] and antineoplastic[58] therapeutic agents. Over the last few decades, deoxynucleosides have attracted the attention of many research groups due to their antiviral and antitumor activities. They are also important components of antisense oligonucleotides.

The 2′-deoxynucleosides such as 3′-azido-2′,3′-dideoxythymidine (AZT), 2′,3′-dideoxyinosine (ddI), 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T) and related analogues have shown potent antiviral activity, particularly against human immunodeficiency virus (HIV) (Fig. 4), which is the causative agent for acquired immune deficiency syndrome (AIDS).[59]

Nucleosides are generally considered to be compounds which contain a heterocyclic aglycon and a carbohydrate moiety that are joined together by a carbon–nitrogen bond. However, *C*-nucleosides differ from the more common nucleosides in that the sugar and heterocyclic aglycon are connected by a C–C, rather than a C–N, bond.[60] From the last few years synthesis of C or N-nucleosides and nucleoside analogues by utilizing furanoid glycals as the key intermediates has also received much attention in research. In this overview we have discussed as one of the important application of furanoid glycals for synthesis of C and N-nucleosides.

To synthesize different *C*-nucleosides Daves Jr and his group contributed a lot in the field of nucleoside chemistry by utilizing differently substituted furanoid glycal.

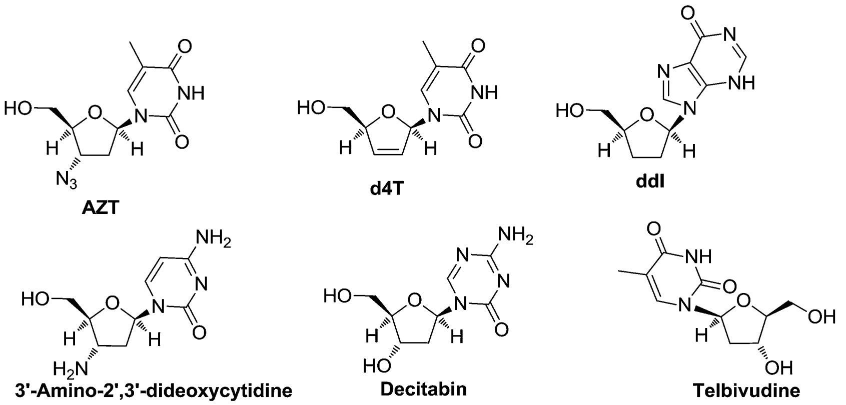

Fig. 4 Structures of some 2′-deoxynucleosides have potent antiviral activity, particularly against human immunodeficiency virus (HIV).

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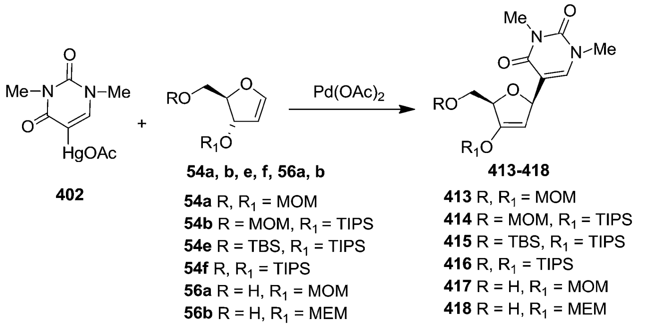
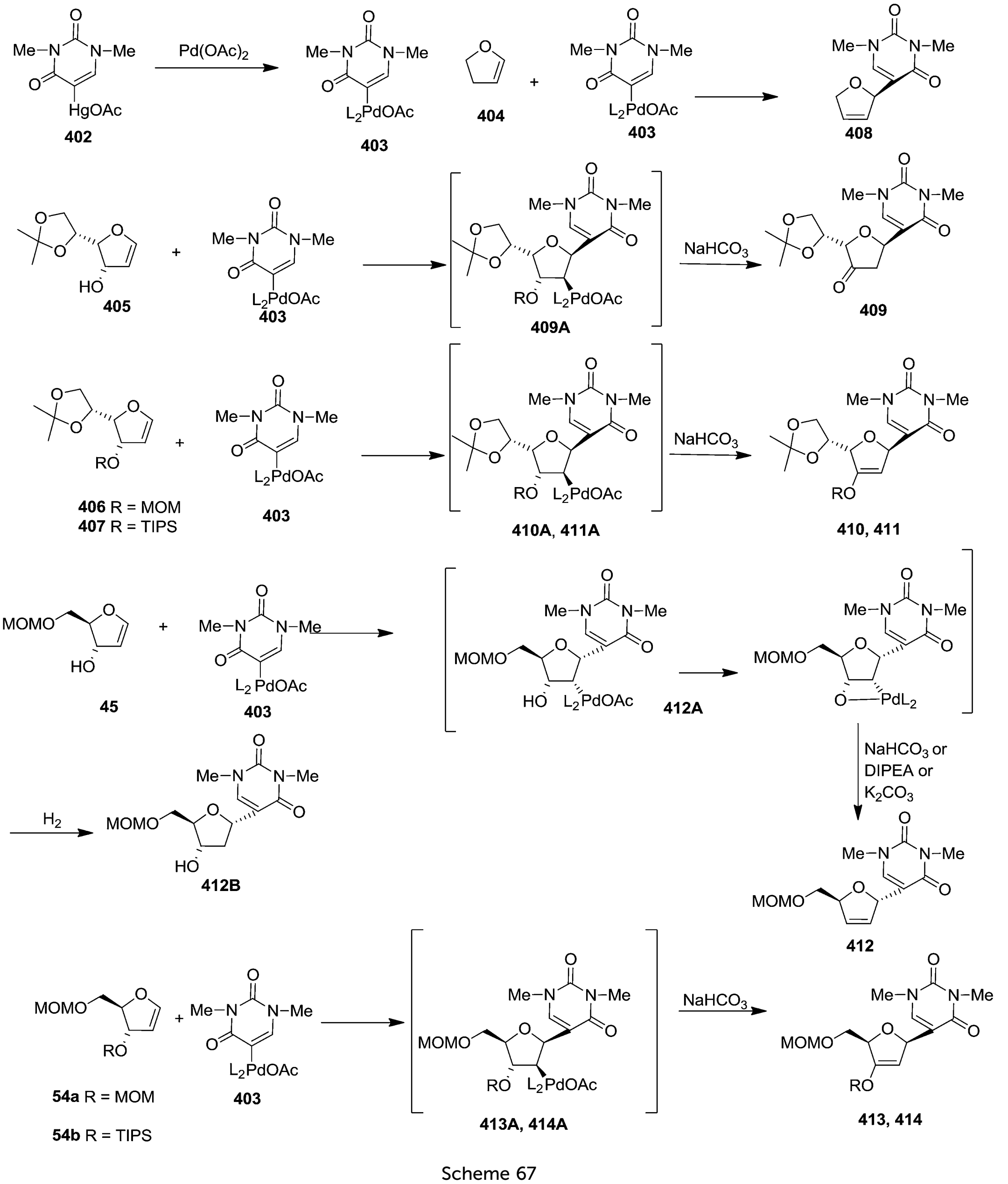
In 1983 Daves Jr and Hacksell showed Heck coupling reactions of furanoid glycals **404–407, 45, 54a, 54b** with (1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrimidin-5-yl)mercuric acetate **402** in the presence of a stoichiometric quantity of $Pd(OAc)_2$ resulted in regio- and stereospecific formation of α or β-*C*-nucleosides (**408–414**) through an initial transmetalation leading to an organopalladium reagent which subsequently adds to the olefinic double bond in a *syn* fashion to form adducts (**409A–414A**) (Scheme 67).[6] These are reasonably stable and decomposed to α- or β-*C*-nucleosides (**409–414**) *via syn* elimination of hydropalladium. The more stable adduct **412A** among them on treatment with hydrogen for 8 h was resulted in 2′-deoxy C-nucleoside **412B**. In this report, they demonstrated the direction of addition of organopalladium reagent to *trans*-substituted furanoid glycals (**45, 54a, 54b**) which was depended



Scheme 68



Scheme 67

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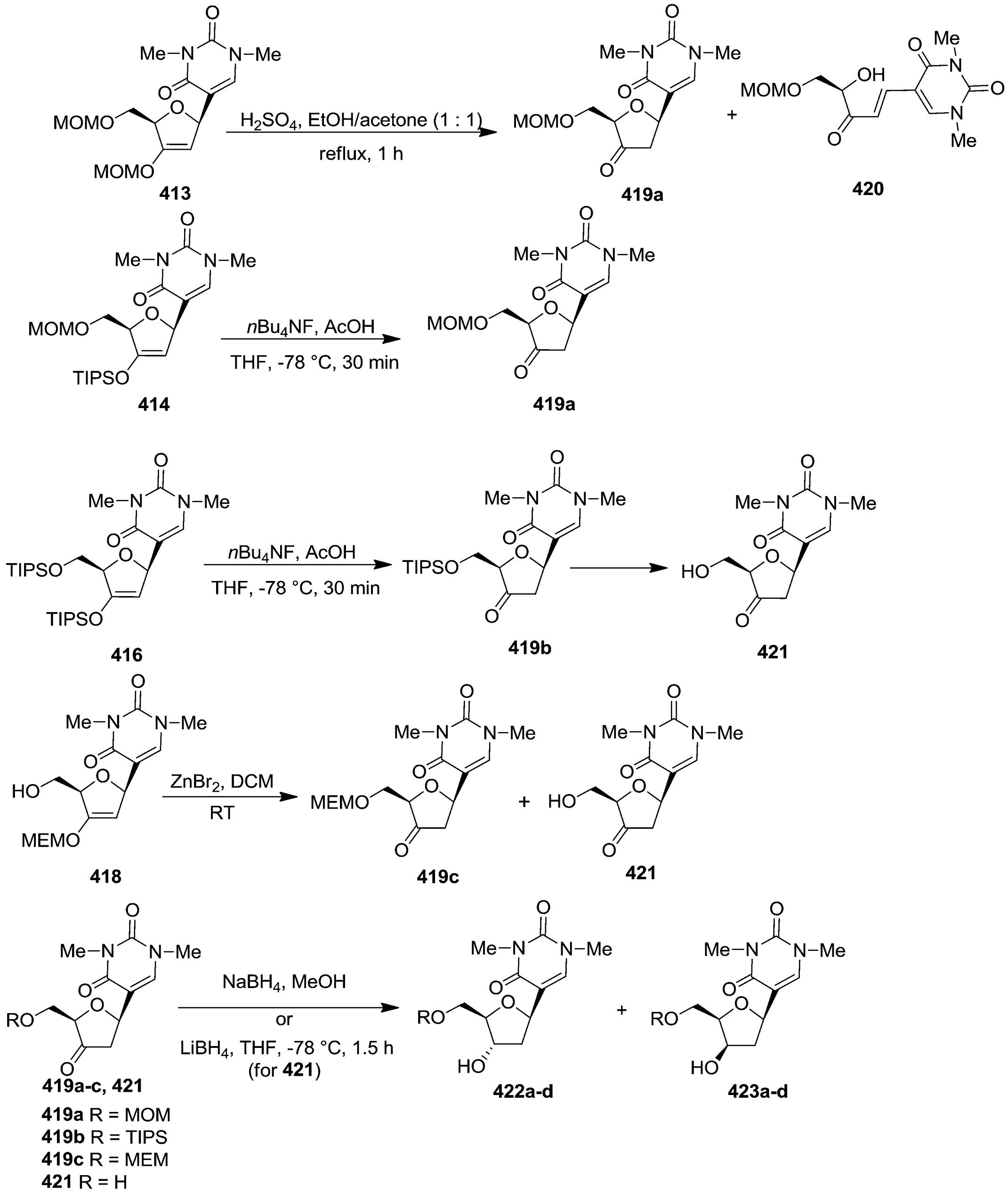
on the steric bulk of C3 and C4 substituents of the corresponding *trans*-furanoid glycals to form *C*-nucleosides (**412–414**). Organopalladium reagent always attacked from less sterically hindered site of the furanoid glycals. With *cis*-substituted glycals (**405–407**), the attack occured on the unsubstituted face of the ring to form *C*-nucleosides (**409–411**).

This research group after reported the synthesis of differently substituted furanoid glycals[20a] and α-or β-*C*-nucleosides, they further extended their study to show that when both the 3- and 5-hydroxyls are identically substituted *e.g.* **54a** and **54f**, the organopalladium reagent attacked from β-face to form **413** and **416** respectively. Thus, it indicated that the reaction was more sensitive to the steric bulk of the substituent at the allylic position (C3) than to that at position C5 of the furanoid glycal. Use of very bulky group at C3 for **54b**, **54e** also yielded β-*C*-nucleoside **414**, **415** respectively. The furanoid glycals **56a** and **56b** whose 3-OH was substituted and 5-OH was free led only to β-*C*-nucleosides **417** and **418** respectively (Scheme 68).[61]

The methoxymethyl group of *C*-nucleoside of **413** was removed under acidic condition to form **419a** and/or **420**. *O*-trialkylsilyl β-*C*-nucleosides **414** and **416** on treatment with TBAF in the presence of AcOH in THF at −78 °C yielded **419a** and **419b** and/or **421** respectively. The removal of (β-methoxyethoxy)methyl group in **418** by using zinc bromide[14] resulted in migration of the (β-methoxyethoxy)methyl group from the 3′-*O* to the 5′-*O* to form **419c** along with **421**.



Scheme 69

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Table 8 Borohydride reduction of (**419a–c**, **421**)

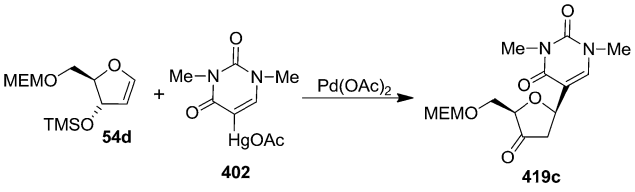
Entry	3′-Keto-*C*-nucleoside	R	Reducing agents	Temperature °C	Yield^a%	3′-OH$_\alpha$/3′-OH$_\beta$^{b}	Products
1	**419a**	MOM	$NaBH_4$	0 °C	73	1 : 3	**422a/423a**
2	**419b**	TIPS	$NaBH_4$	0 °C	88	1 : 2	**422b/423b**
3	**419c**	MEM	$NaBH_4$	−78 °C	55	1 : 2	**422c/423c**
4	**421**	H	$LiBH_4$	−78 °C	60	1 : 2	**422d/423d**

[a] Isolated yield. [b] Determined by high-pressure liquid chromatography.

The borohydride reduction of (**419a–c**, **421**) gave separable α-3′-hydroxyl (**422a–d**) and β-3′-hydroxyl derivatives (**423a–d**) (Scheme 69, Table 8).

The furanoid glycal **54d** on Pd-mediated coupling reaction with **402** yielded a 3′-keto-β-*C*-nucleoside **419c** which indicated that the trimethylsilyloxy substituent effectively directed organopalladium adduct formation even though trimethylsilyl was lost during reaction (Scheme 70).

Coupling of **402** with 3,5-*O*-unsubstituted glycal (1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol) **55** produced a mixture of the α- and β-*C*-nucleosides **421** and **424** in 45% and 29% yields, respectively. Coupling of **402** with 5-*O*-substituted glycal **53c** gave α-*C*-nucleoside **424** as the sole product *via* formation of **425** followed by desilylation (Scheme 71).

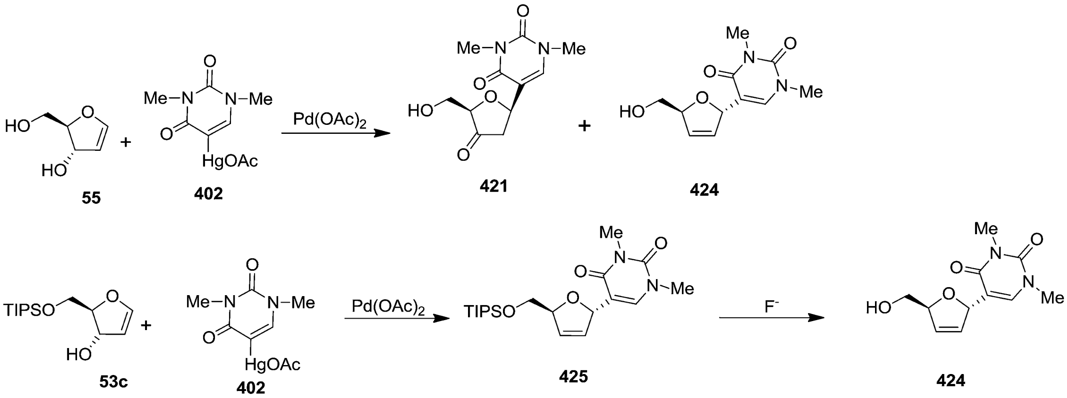


Scheme 70

Daves Jr and Outten further utilized their developed methodology for coupling of furanoid glycals with 1-methoxy-4-(tri-*n*-butylstannyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one for synthesis of benzo[*d*]naphtho[1,2,-*b*]-pyran-6-one-*C*-glycosides related to antibiotics ravidomycin, gilvocarcins (toromycin), and chrysomycin A and B (virenomycin) for the very first time. 1-Methoxybenzo[*d*]-naphtho[1,2-*b*]pyran-6-one **426** was brominated at *para* position to –OMe with NBS in DMF at room temperature for 30 min to give **427** in 81% yield, which on treatment with hexa-*n*-butylditin $(nBu_3Sn)_2$ in the presence of 2.0 mol% of $Pd(PPh_3)_4$ in toluene (N_2, 115 °C, 12 h) produced stannane **428** in 65% yield. Its coupling with furanoid glycal **54b** in the presence of stoichiometric $Pd(OAc)_2$ in CH_3CN at room temperature for 24 h furnished *C*-glycoside **429** in 66% yield. Similar coupling of **428** with glycal **54f** formed the corresponding *C*-glycoside **430** in a 28% yield. Silyl ether deprotection of **429** and **430** by nBu_4NF in the presence of acetic acid in THF at room temperature for 2 h yielded the corresponding 3′-keto-*C*-glycosides **431** (94%) and **432** (92%) respectively. Reduction of the ketones **431** and **432** with $NaBH_4$, H_2O in tetrahydrofuran afforded the corresponding 2′-deoxy-*C*-glycosides **433** and **434** respectively (Scheme 72).[62]

Daves Jr discussed coupling reaction of iodo derivatives of anthracycline aglycons with furanoid and pyranoid glycals in stoichiometric amounts in the presence of catalytic amounts of palladium(II) acetate and a tertiary amine in DMF at room temperature to get regio and stereospecific aryl *C*-glycosides.[63] After several trial and error, they treated anthracycline iodo derivative **435** with furanoid glycal **54b** in the presence of 10 mol% $Pd(OAc)_2$, 2 equiv. of nBu_3N, and 1 equiv. of NaOAc in DMF at room temperature for 48 h to furnish *C*-glycoside **436**, which was *in situ* desilylated under the reaction condition to afford 3′-keto-β-*C*-glycoside **437** in 85% yield. This reaction was equally successful with tetra-*n*-butylammonium chloride and sodium bicarbonate (Scheme 73).

They have also synthesized *C*-glycoside **440** from furanoid glycal **66o** in a one pot three step sequence. Under the identical



Scheme 71

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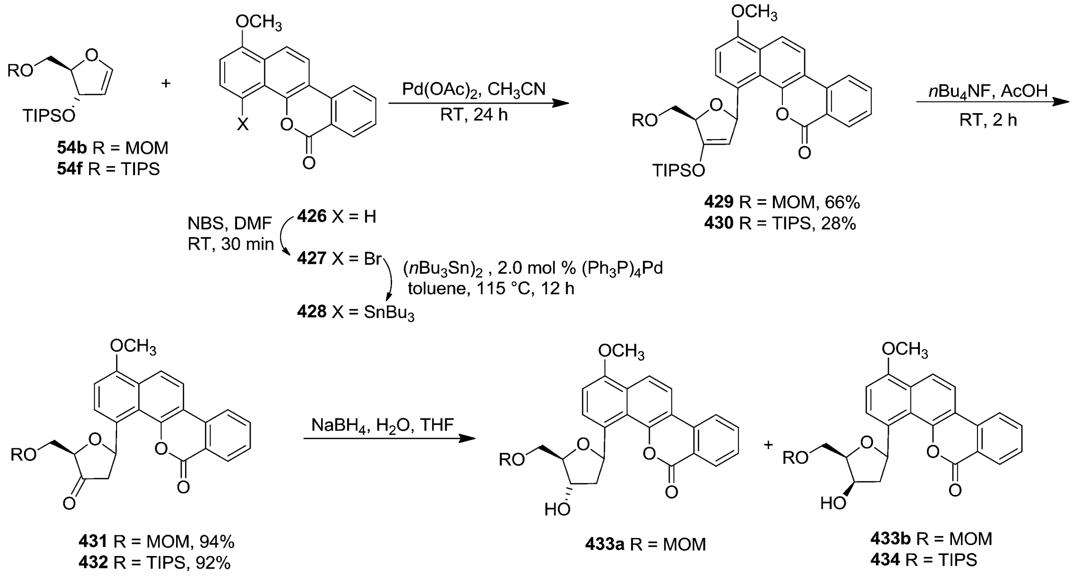
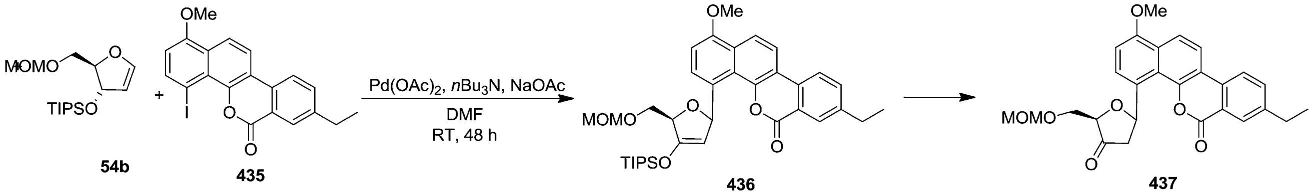
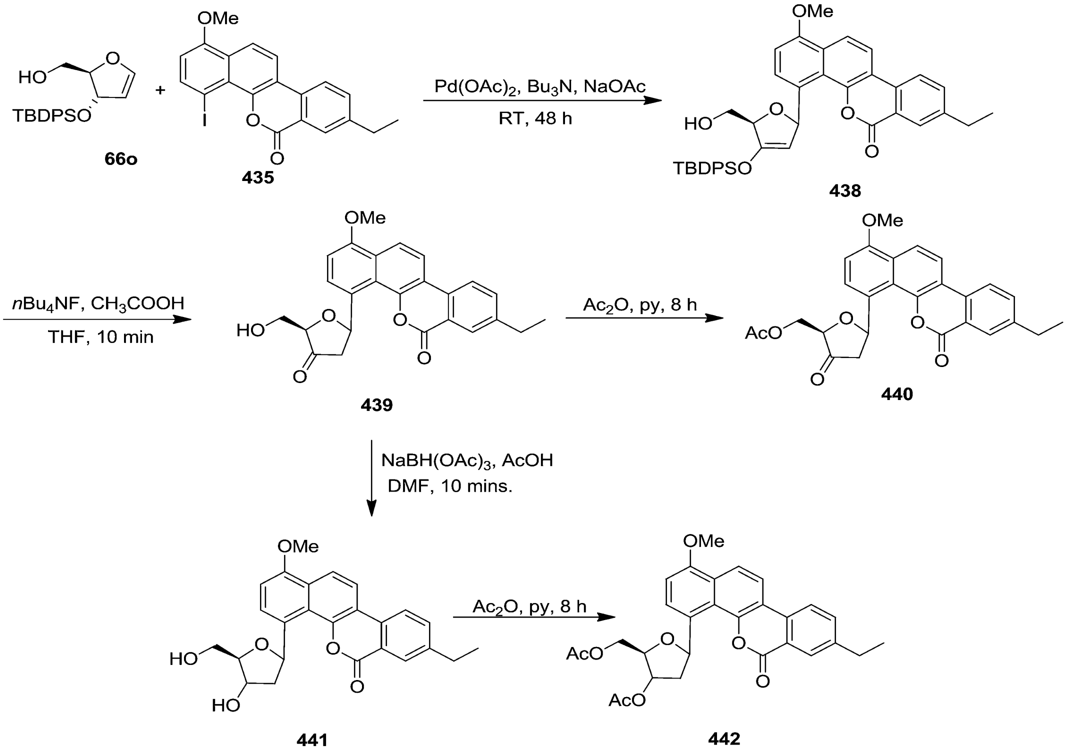


Scheme 72



Scheme 73



Scheme 74

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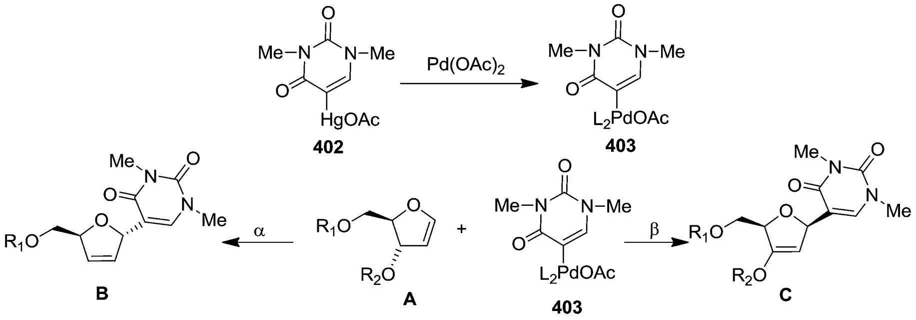


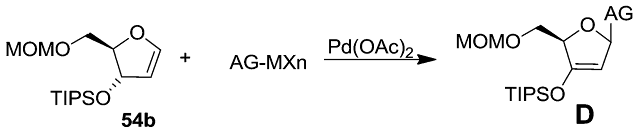
Scheme 75

palladium-catalyzed coupling reaction condition, furanoid glycal **66o** was stirred with iodo anthracycline **435** for 10 h at room temperature to form **438**, which was then desilylated by the nBu$_4$NF in reaction medium to give keto derivative **439**. The free –OH group was then acetylated into the same reaction medium to furnish *C*-glycoside **440** in 89% isolated yield by one pot three step sequence. The stereospecific reduction of a 3′-keto group of a furanosyl *C*-glycoside **439** with NaBH(OAc)$_3$ gave **441** which was acetylated to *C*-glycoside **442** in 94% isolated yield by one-pot four-step sequence (Scheme 74).

In 1990 Daves Jr discussed the regio- and stereospecific synthesis of *C*-glycosides by palladium-mediated coupling reaction of glycals (furanoid or pyranoid glycal), with suitable aglycon (heterocyclic or anthracyclic) derivatives.[64] The reaction of pyrimidine mercurial derivative **402** with Pd(II) acetate led to the formation of Pd(II) organopalladium reagent **403**, which underwent stereospecific coupling reaction with furanoid glycals (**55**, **56a**, **45**, **54a**, **54b**, **54f**, **66o**) to yield single product (either a α-*C*-glycoside or a β-*C*-glycoside, Table 9). They observed in the case of **56a**, **45** or **66o** where only one of the two glycal hydroxyls was substituted, the π-complex was formed exclusively from the face of the furanoid ring opposite to the substituted hydroxyl to give **417**, **412** and **444** respectively. When both glycal hydroxyls were substituted (**54a**, **54b**, or **54f**), the organopalladium reagent attacked from the β-face of the glycal to form **413**, **414**, **416** respectively, indicated that the reaction was more sensitive to the steric bulk of the C3 substituent than to that at position C5 of the furanoid glycal. Only when both hydroxyls of the glycal remain unsubstituted **55** mixture of stereoisomeric *C*-glycosides **443a** and **443b** were obtained (Scheme 75, Table 9).

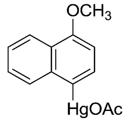
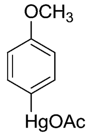
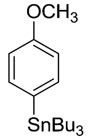
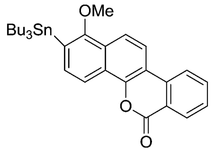
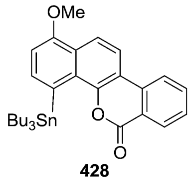
Table 9 Stereochemistry of *C*-glycoside formation by palladium-mediated glycal aglycon coupling

Entry	% yield of α-*C*-nucleosides (**B**)	Substituents of (**A**)	% yield of β-*C*-nucleosides (**C**)
1	29 (**443a**)	**55** $R_1 = R_2 = H$	45 (**443b**)
2	0	**56a** $R_1 = H$, $R_2 = MOM$	65 (**417**)
3	78 (**412**)	**45** $R_1 = MOM$, $R_2 = H$	0
4	0	**54a** $R_1 = R_2 = MOM$	71 (**413**)
5	0	**54b** $R_1 = MOM$, $R_2 = TIPS$	92 (**414**)
6	0	**54f** $R_1 = R_2 = TIPS$	51 (**416**)
7	0	**66o** $R_1 = H$, $R_2 = TBDPS$	84 (**444**)



Scheme 76

Table 10 Coupling reactions of aglycon-mercuric acetate and tri-*n*-butylstannyl derivatives with a furanoid glycal **54b** in the presence of stoichiometric Pd(OAc)$_2$

Entry	AG-MX$_n$	*C*-Glycoside product, % yield (**D**)
1	 **445**	96
2	 **446**	57
3	 **447**	70
4	 **448**	57
5	 **428**	66

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In this report, Daves Jr also showed the comparative study of coupling reaction of aglycon-mercuric acetate and tri-*n*-butylstannyl derivatives with a particular furanoid glycal **54b** in the presence of stoichiometric Pd(II) acetate and observed there were no significant differences in the effectiveness (Scheme 76, Table 10).

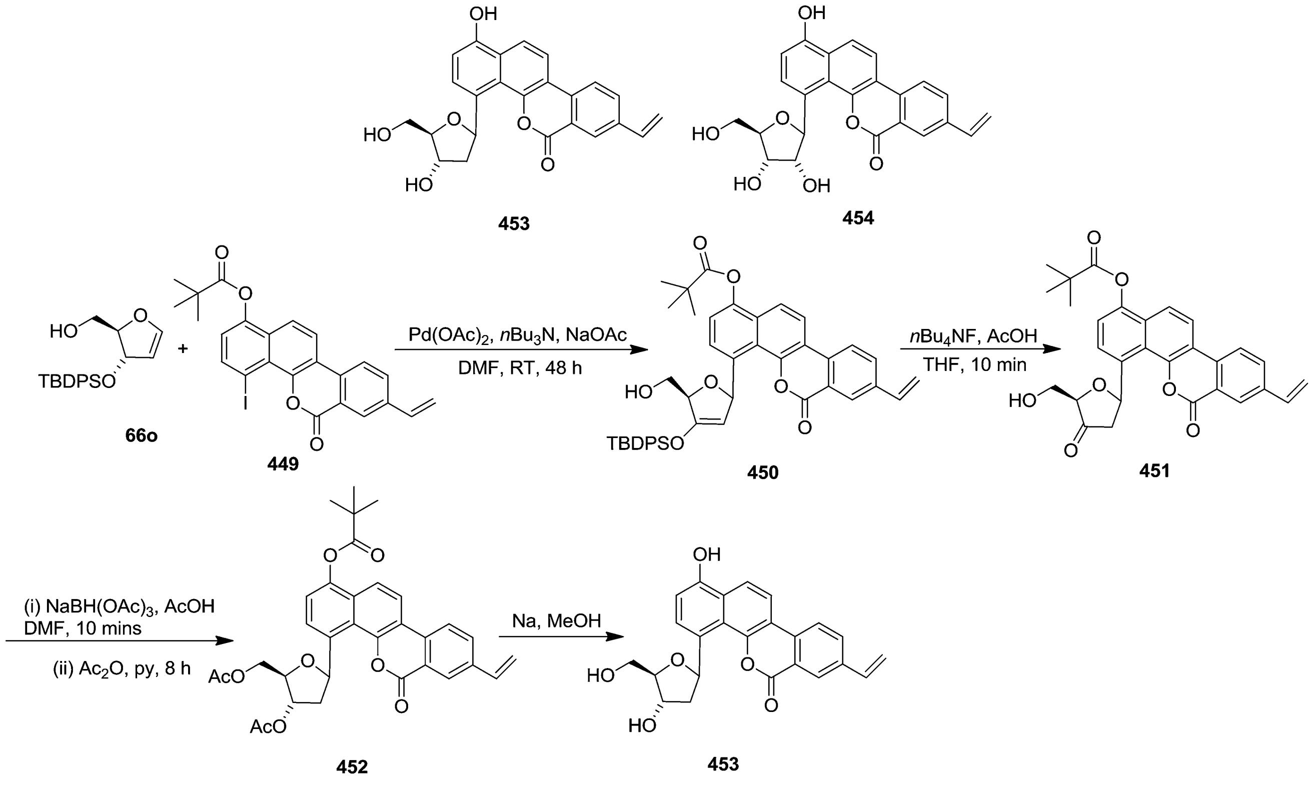
In 1992, this research group further reported syntheses of synthetic *C*-glycosides **453** and **454** structurally related to the gilvocarcin, ravidomycin, and chrysomycin antibiotics which possess the aglycon substituents (hydroxyl at C-1 and ethenyl at C-8) considered critical for the photolytic nicking of DNA. They synthesized β-*C*-glycosides **453** from triester **452** (Scheme 77) which was synthesized following the same one-pot four-step sequence from furanoid glycal **66o** and pivaloyl protected aglycon derivative **449**.[65]

They further extended their study and showed the utility of regio- and stereospecific *C*-glycosyl bonds formation by the synthesis of *C*-nucleoside analogs. They synthesized 2′-deoxypseudouridin **458** in three steps by utilizing the palladium-mediated coupling of 5-iodouracil **455** with glycal **66o**, as the key step in the presence of either triphenylphosphine or triphenylarsine ligands. The coupling reaction formed β-*C*-nucleoside **456** which, without isolation, was desilylated with fluoride ion to form the 2′-deoxy-3′-keto-*C*-nucleoside **457**. Finally, stereospecific reduction of the 3′-keto group with NaBH(OAc)$_3$ formed 2′-deoxypseudouridine **458** (Scheme 78).[66]

In a similar way, they synthesized 2′-deoxyformycin B **463**, 2′,3′-dideoxyformycin B **468** by palladium-mediated glycal-aglycon coupling reaction as the key step. Ribofuranoid glycal **66o** and bis(tetrahydropyranyl) protected iodo aglycon derivative **459** underwent regio and stereospecific coupling reaction in the presence of Pd(dba)$_2$ as catalyst and triphenylarsine as ligand in acetonitrile to give *C*-nucleoside **460** in 62% isolated yield. Following the similar reaction sequence desilylation followed by stereospecific keto group reduction, *C*-nucleoside **460** was converted to **462** *via* **461** which on treatment with pyridinium *p*-toluenesulfonate yielded 2′-deoxyformycin B **463** in 83% yield (Scheme 79).[66]

2′-Deoxy-*C*-nucleoside **462** was transformed into 2′,3′-dideoxyformycin B **468** in five steps in 52% overall yield. The primary hydroxyl at C-5′ was selectively silylated to form **464** followed by protection of the C-3′ hydroxyl using *O*-phenyl chlorothionoformate to give intermediate **465** which on deoxygination with nBu$_3$SnH/AIBN produced 2′,3′-dideoxy *C*-nucleoside **466**. Its silyl ether deprotection with fluoride ion furnished **467** which on removal of tetrahydropyranyl groups with pyridinium *p*-toluenesulfonate afforded 2′,3′-dideoxyformycin B **468** (Scheme 80).[66]

Daves Jr have reported the synthesis of 1-(tri-*n*-butylstannyl) furanoid glycals for the first time by lithiation of the corresponding 3-*O*-unsubstituted glycals (**404**, **469**, **55**, **53b**) followed by reaction with nBu$_3$SnCl. They also discussed the tri-*n*-butylstannaylation of 3-*O*-substituted hydroxy glycal **66h**, which underwent elimination to yield the corresponding furan in the presence of *t*BuLi. Finally, they succeeded to prepare 3-*O*-benzyl furanoid glycal **478** from phenylthioglycoside **475**, which was oxidized with *m*-CPBA to phenyl sulfone **476**. Treatment of **476** with *n*BuLi furnished unsaturated sulfone **477**, which was



Scheme 77

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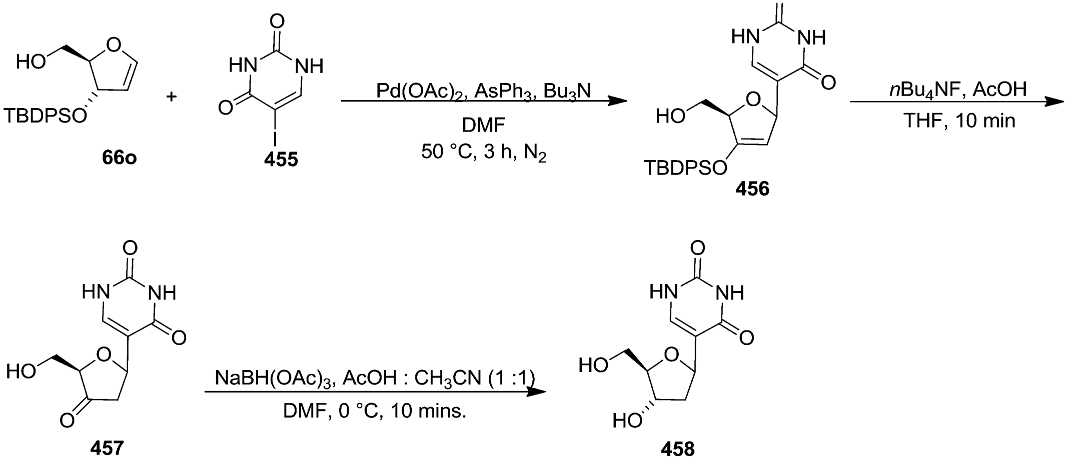
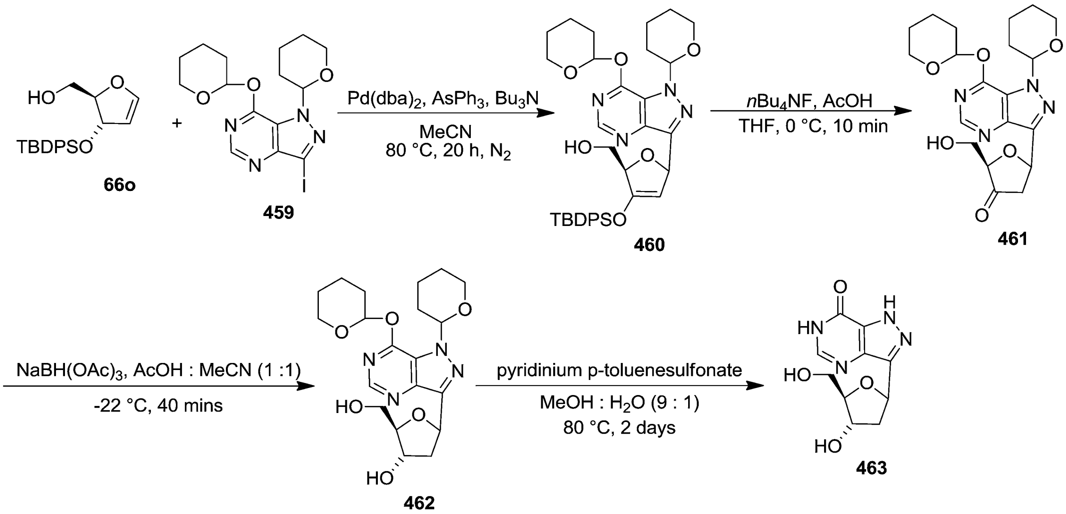
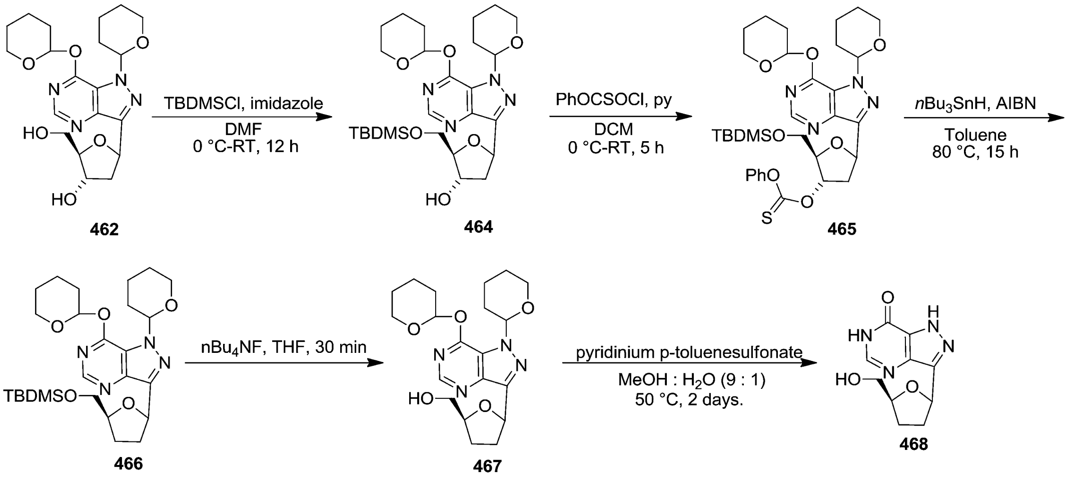


Scheme 78



Scheme 79



Scheme 80

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treated with $n\mathrm{Bu_3SnH}$ in the presence of AIBN formed stannylated 3-*O*-benzyl furanoid glycal **478**. Palladium mediated coupling reaction of these stannylated furanoid glycals (**470–473, 478**) with iodoaglycon derivatives yielded the corresponding 1-substituted furanoid glycals in good to excellent yields (Scheme 81).[67]

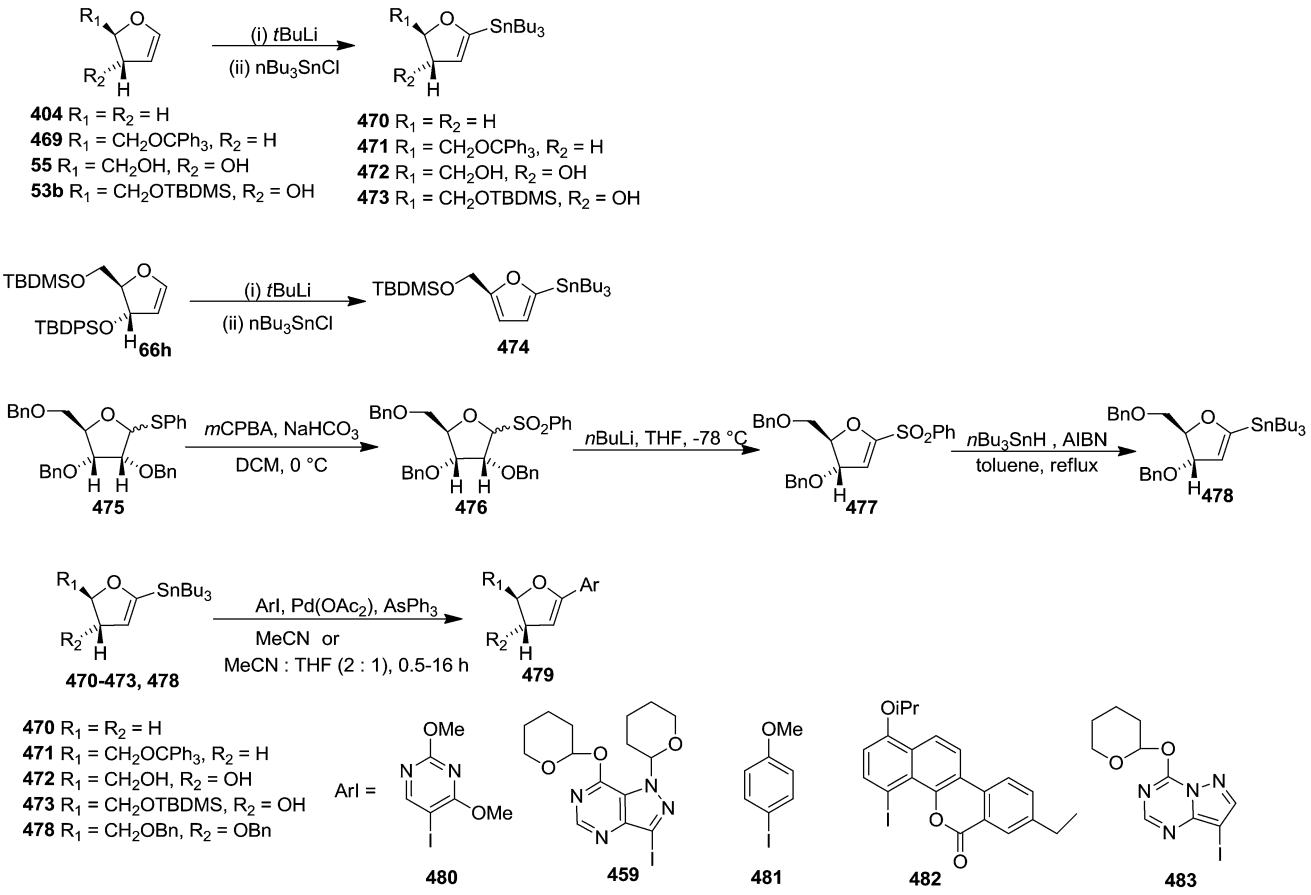
This group further extended their studies on Pd-mediated regio- and stereospecific coupling reaction of **483** with furanoid glycal **56a** to obtain *C*-nucleosides **484**.[68] The coupling of iodoaglycon derivative **483** with furanoid glycal **66o** followed by desilylation of **485** with TBAF and stereospecific hydroxy-activated reduction of the 3′-keto group of intermediate **486** using $\mathrm{NaBH(OAc)_3}$ yielded the 2′-deoxyribofuranosyl *C*-nucleoside **487** in 65% yield for the three steps (Scheme 82).

Similarly, they synthesized palladium-mediated coupling of 8-iodo-4-methoxypyrazolo[1,5-*a*]-1,3,5-triazine **488** and furanoid glycal **66o** efficiently produced *C*-nucleoside intermediate **489** which was desilylated to form 3′-keto *C*-nucleoside **490** (Scheme 83).

They also tried Pd-mediated coupling of iodoaglycon **491** and **492** with furanoid glycal **66o** but it was futile. As a result, they prepared aglycon bis-carbamate derivative **494** by reaction of **493** with isobutyloxycarbonyl chloride in the presence of pyridine. Aglycon derivative **494**, was successfully coupled with glycal **66o** in the presence of catalytic $\mathrm{Pd(dba)_2}$ and $\mathrm{AsPh_3}$ to give, after desilylation of the initially formed silyl enol ether with fluoride ion, 3′-keto *C*-nucleoside **495** (2 steps, 50% yield) (Scheme 84).

In the same year, Townsend and group reported an efficient and stereospecific synthesis of pyrazine *C*-nucleosides by Pd(0)-mediated cross-coupling reaction between ribofuranoid glycals **66e**, **66f** and **65b** and iodoaglycon **496**.[69] The cross-coupling reaction between aglycon **496** and ribofuranoid glycal **66e** resulted silyl enolether derivative **497a** which was gradually converted to **498a.** Pd-mediated cross-coupling reaction between iodoaglycon **496** and ribofuranoid glycal **66f** furnished *C*-nucleoside **497b** whereas under identical reaction condition furanoid glycal **65b** only resulted in the isolation of the 2′-deoxy-3′-keto-*C*-nucleoside **498b** instead of the silyl enol ether derivative **497c.** They selectively deprotected the 3′-silyl group of the silyl enol ethers **497a** and **497b** by the fluoride ion at low temperature to give **498a** and **498b**, respectively. 2′-Deoxy-β-D-ribofuranoside **500** was prepared from the complete deprotection of **497a**, **b** or **498a**, **b** with TBAF *via* **499**, followed by a stereospecific reduction by $\mathrm{NaBH(OAc)_3}$. They confirmed the β-configuration of *C*-nucleoside **500** by NOE analysis and also converted it to 5,5′-anhydro nucleoside **501** by diazotization reaction with iso-amyl nitrite (Scheme 85).

Motivated by the work of Daves *et al.*, in 1995, McLaughlin and coworkers reported the synthesis of two pyridine *C*-



Scheme 81

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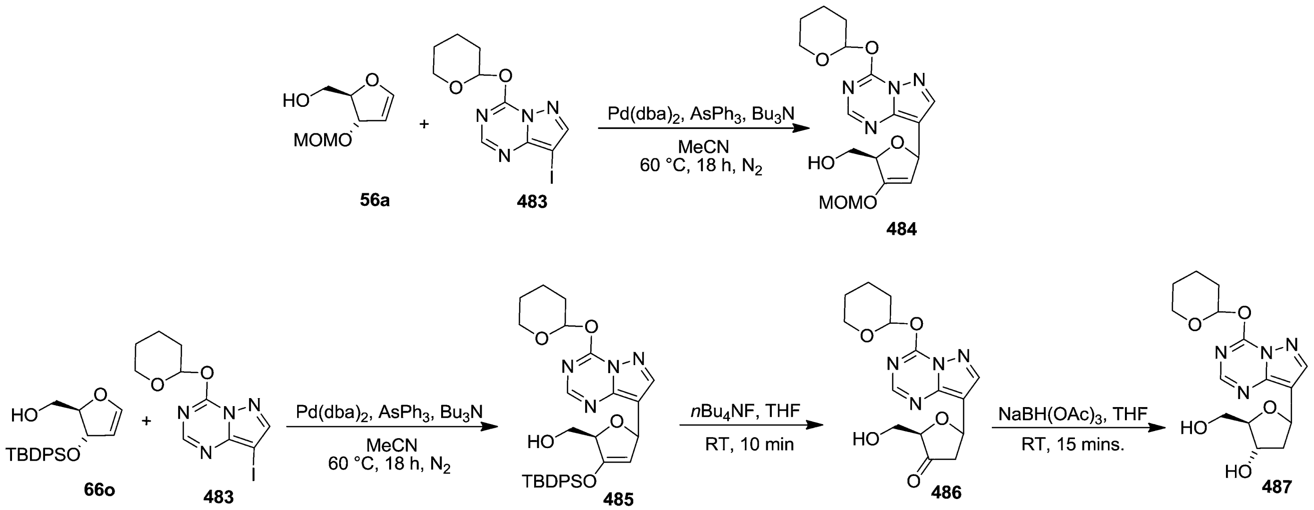
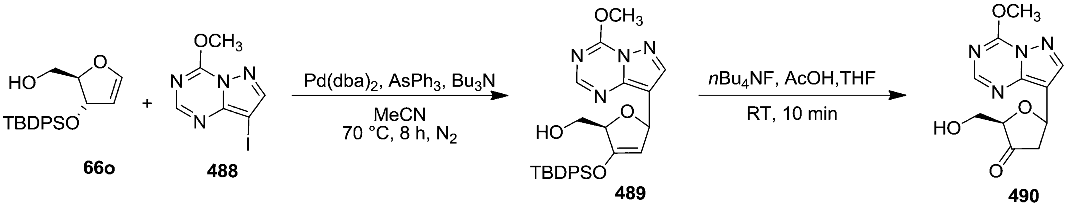
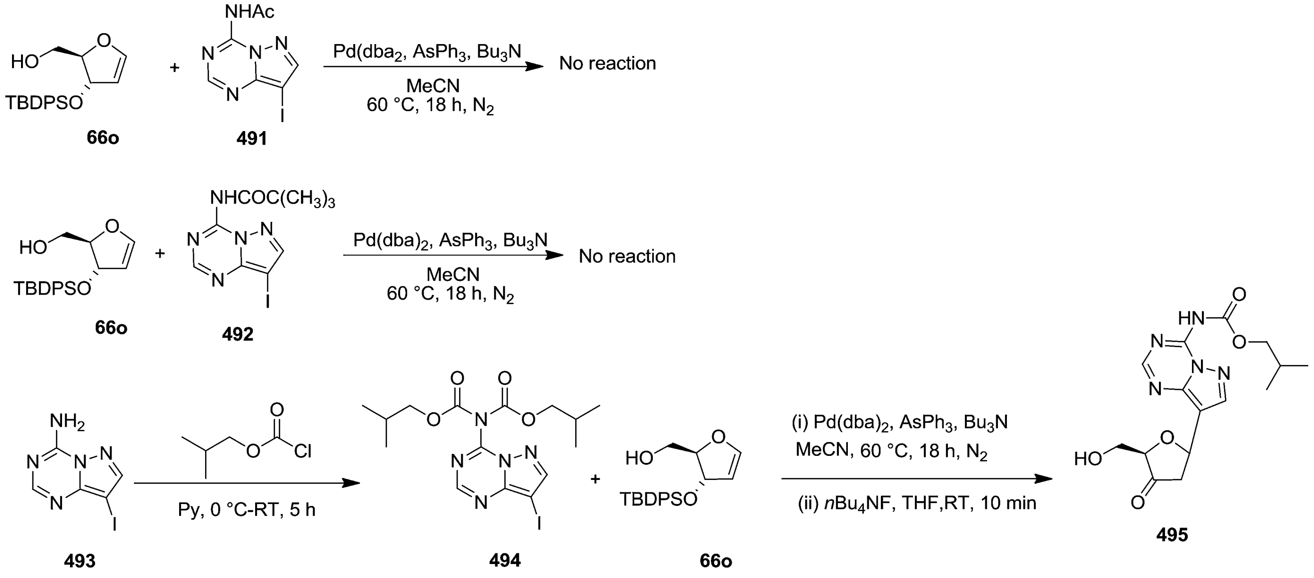
nucleosides **507** and **512**, "deletion modified" analogues of dT and dC.[70] After several trial and error, they prepared 2-(benzyloxy)-3-methyl-5-iodopyridine **505** from **502** in three steps. Pd-mediated coupling reaction of glycal **66o** and 2-(benzyloxy)-3-methyl-5-iodopyridine **505** in the presence of ancillary ligand 1,3-bis(diphenylphosphino)propane resulted *C*-nucleoside **506** in 90% yield. *C*-Nucleoside **506** was then converted into **507** by three steps sequential reactions, silyl ether deprotection, followed by stereoselectively keto group reduction



Scheme 82



Scheme 83



Scheme 84

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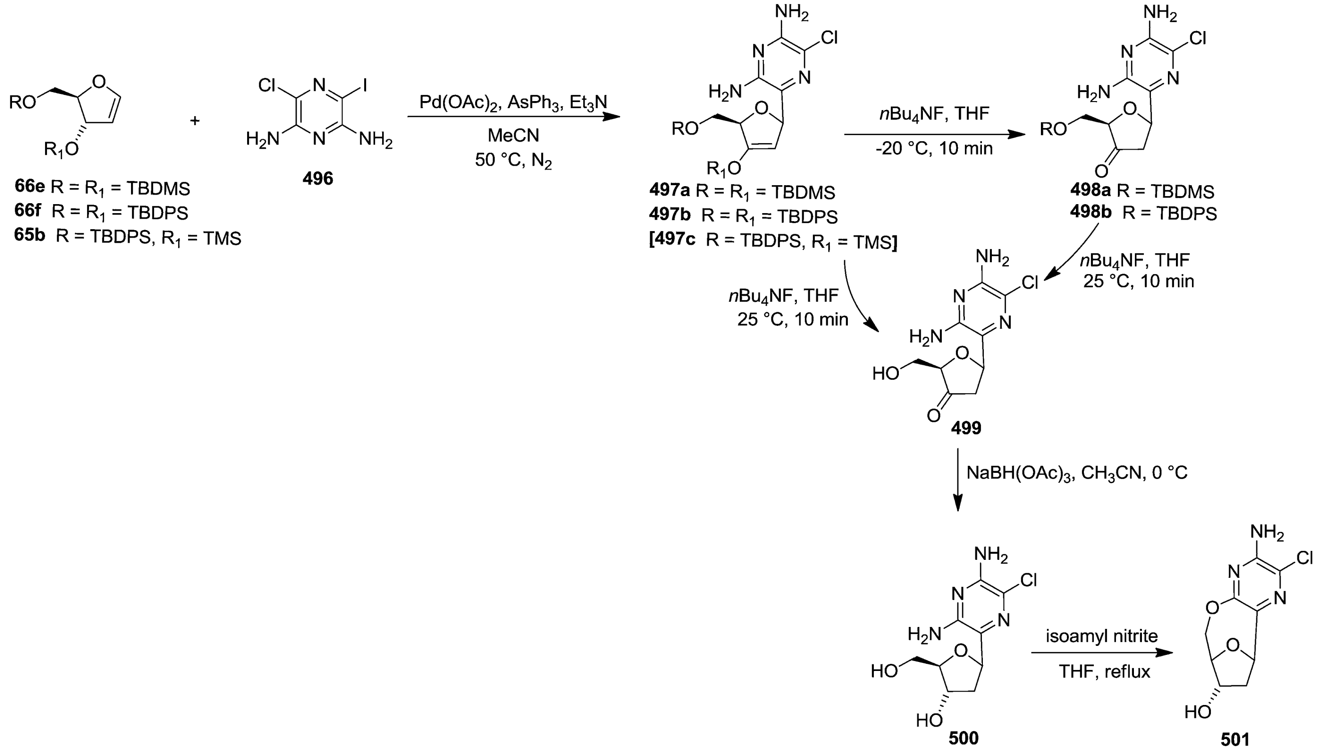
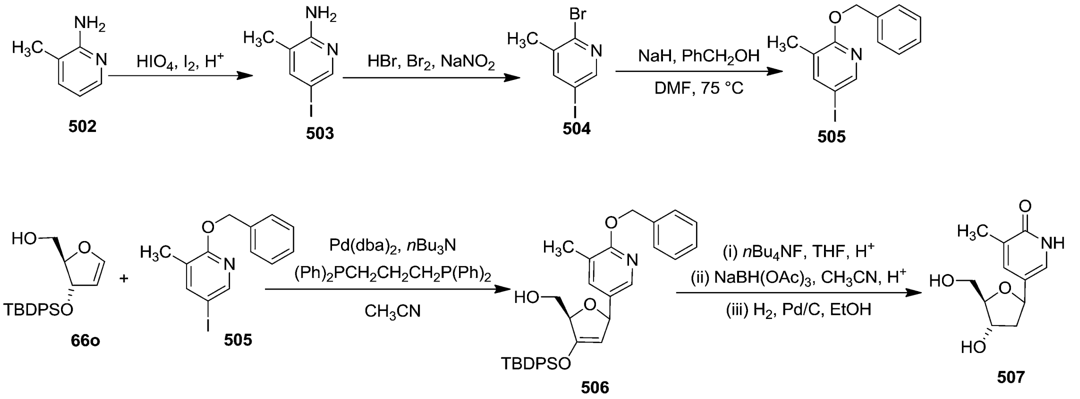


Scheme 85



Scheme 86

and finally benzyloxy group deprotection by catalytic hydrogenation (Scheme 86).

In a similar fashion, they prepared the *C*-nucleoside analogue of dC **512** from 2-aminopyridine **508**. They prepared **510** from **508** by its iodination followed by amino group protection with BzCl of the resulting iodo derivative **509**. The coupling reaction of glycal **66o** with **510** in the presence of Pd and an ancillary ligand $P(C_6F_5)_3$ resulted in moderate yields of product **511** (36% yield). The remaining steps to generate **512** were strictly analogous to those described in Scheme 86 for the synthesis of **507** (Scheme 87).

In 1998, Coleman and Madaras followed Daves Jr strategy for synthesis of coumarin β-*C*-riboside **522**. For this, they synthesized furanoid glycal **66o**,[23] **56a**[20a] and **66n**[23] in the ususal procedure.[71]

Coumarin **515** (X = OH) was prepared from 8-hydroxyjulolidine **513**. Reaction of **513** with bis(2,4,6-trichlorophenyl) malonate **514** in refluxing toluene effected annulation of the α-pyrone ring system to afford **515** in excellent yields (94%). Its hydroxyl functionality could be transformed to the iodide by treating it with a preformed complex of triphenylphosphine and iodine (Ph_3P, I_2, CH_3CN, 82 °C) to form **516**. Alternatively, the hydroxyl group could be acylated with trifluoromethanesulfonic anhydride (Tf_2O, Et_3N, DCM, 0 °C) to afford triflate **517** in 87% yield (Scheme 88). These systems were examined in the Heck coupling reaction with glycals **66o**, **56a** and **66n** (Schemes 89 and 90).

Pd-catalyzed coupling of **516** with glycal **66o** was unsuccessful in providing any of the coupled product **518** (Scheme 89).

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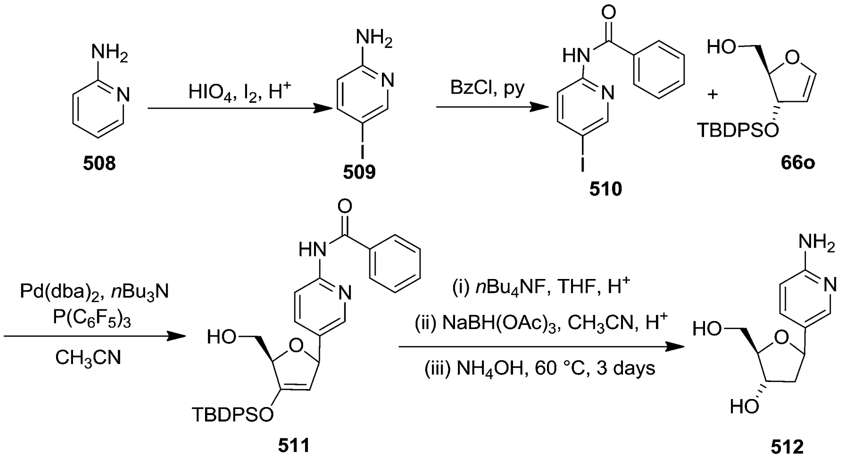
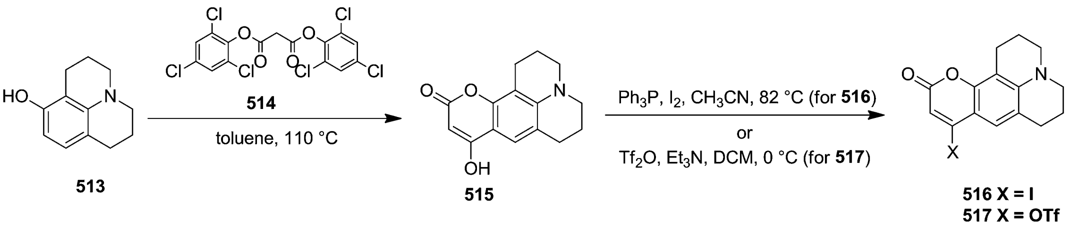
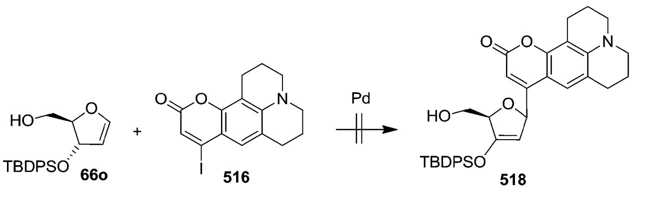


Scheme 87



Scheme 88

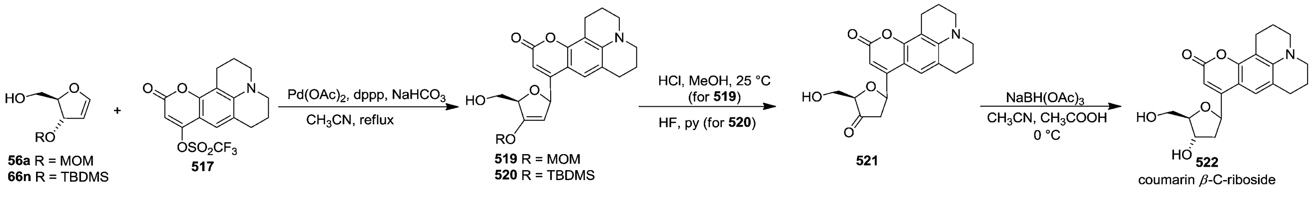


Scheme 89

After getting unsuccessful results, they proceeded for Pd-catalyzed coupling reaction of triflate **517** with glycal **56a** and **66n** in the presence of 40 mol% Pd(OAc)$_2$, 5 mol% dppp, and 3 equiv. NaHCO$_3$ in CH$_3$CN under refluxing condition to obtain Heck product **519** (75% yield) and **520** (79% yield) respectively. Hydrolysis of **519** under acidic conditions (HCl, CH$_3$OH, 25 °C) afforded ketone **521**. Fluoride-promoted cleavage (HF/pyridine) of the silyl ether **520** afforded ketone **521** in excellent yields. The carbonyl group of **521** was reduced stereoselectively to the *ribo*-glycoside **522** with NaBH(OAc)$_3$ (Scheme 90).

In 1999, Tingoli *et al.* showed the reaction of aromatic Grignard reagents with furanoid and pyranoid glycals in the presence of low valent Ni catalyst at low temperature. Treatment of furanoid glycal **90** with aryl magnesium bromide in the presence of Ni(0) catalyst in dry toluene at −10 °C for 5 h afforded column purified 2,3-unsaturated products (**523, 524**) in good yields. They further confirmed the 1,4-*trans* relationship between H-1 and H-4 by NOESY experiment (Scheme 91).[72]

Knaus *et al.* synthesized furanoid glycals (**146a, b**) (Scheme 24), used as key intermediate for the synthesis of unnatural *C*-aryl 2′-deoxy-β-L-cytidine mimics (**529a, b**) (Scheme 92).[32] The Heck coupling reaction of 2,5-difluoro-4-iodoaniline **525a** or 3-fluoro-4-iodoaniline **525b** with glycal **146a** or **146b** in the presence of Pd(OAc)$_2$, Ph$_3$As, and Et$_3$N in dry CH$_3$CN at 70 °C,[32] afforded **526a** (71% yield) or **526b** (57% yield). After several trial and errors, **526b** was subjected to Pd/C catalyzed hydrogenation in anhydrous



Scheme 90

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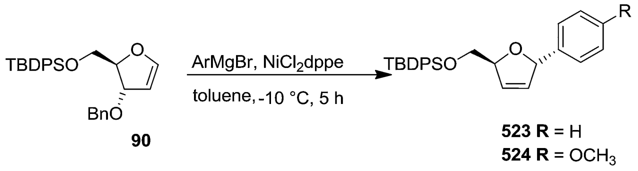
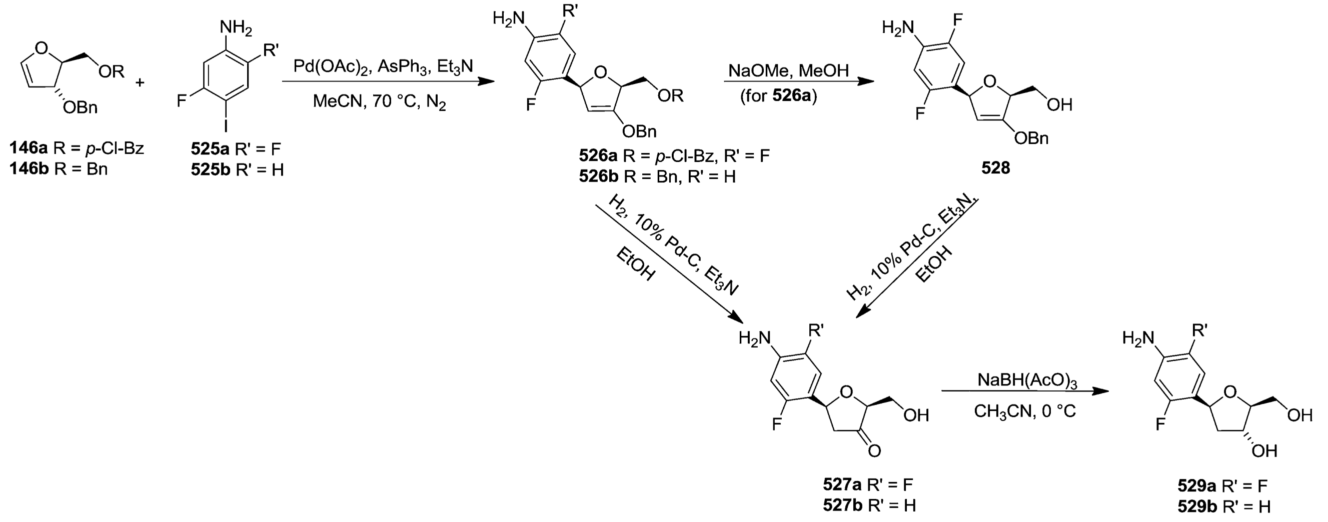
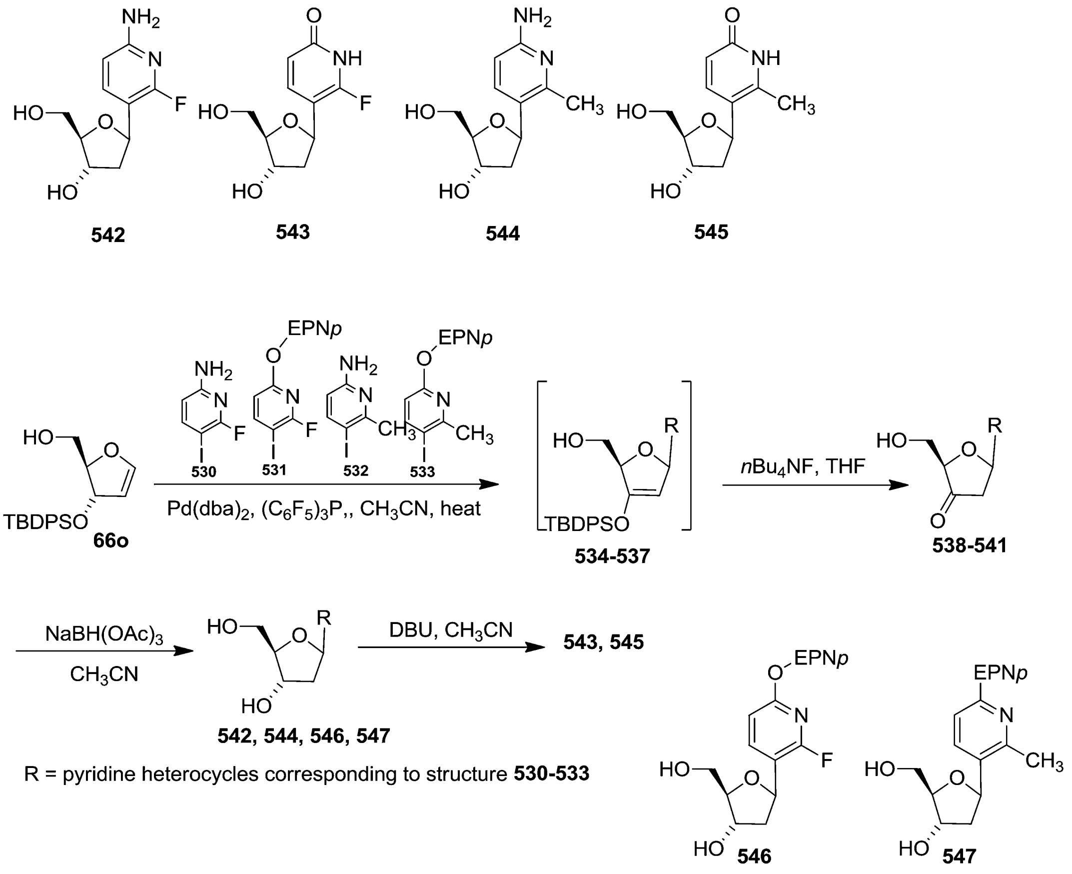


Scheme 91

EtOH containing several drops of Et_3N at 60 °C to afford the hydroxyl ketone **527b** in 61% yield. The 5-(*p*-chlorobenzoyl) group deprotection of **526a** on treatment with NaOMe in MeOH resulted benzyl enol ether **528**, which was converted to the hydroxy ketone **527a** upon Pd/C catalyzed hydrogenation in anhydrous EtOH in the presence of several drops of Et_3N at 60 °C. Subsequent reduction of the hydroxy ketones (**527a, b**) with $NaBH(AcO)_3$ in dry



Scheme 92



Scheme 93

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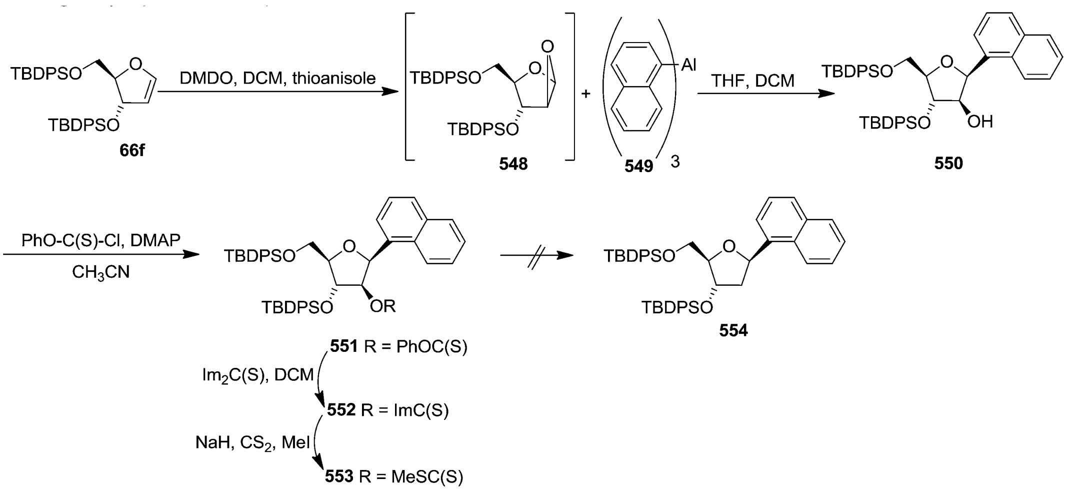
CH_3CN afforded the target deoxy-β-L-cytidine *C*-nucleoside mimics (**529a, b**) (Scheme 92).

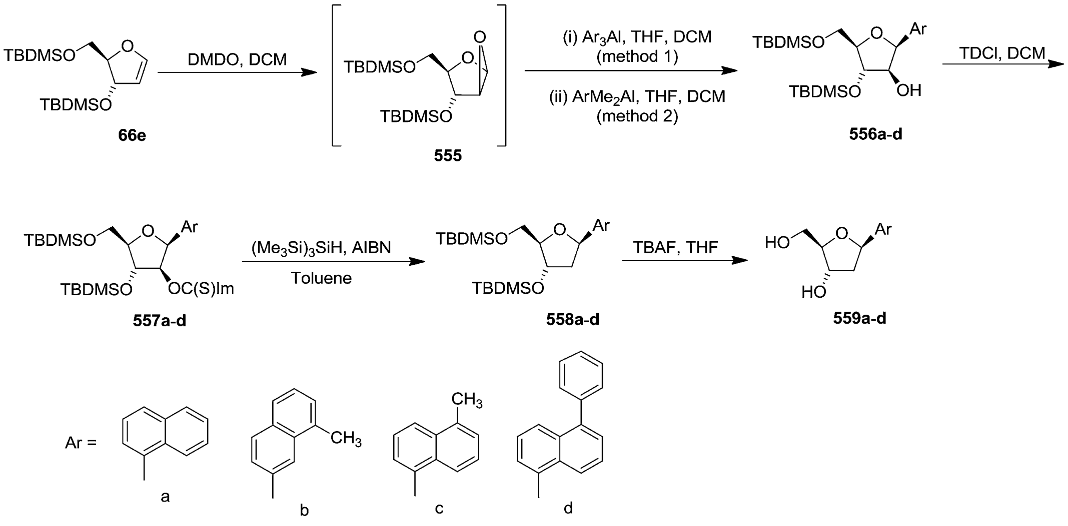
McLaughlin *et al.* described the synthesis of four pyrimidine *C*-nucleoside analogues (**542–545**) of natural nucleosides dC and dU.[73] They synthesized desired pyridine heterocycles (**530–533**) necessary for the syntheses of (**542–545)** from the readily available differently 2,6-substituted pyridines.[73] Furanoid glycal **66o** and pyridine heterocycles (**530–533**) underwent regio and stereospecific Heck-type coupling reaction in the presence of $Pd(dba)_2$ and $(C_6F_5)_3P$ in acetonitrile to give β-*C*-nucleoside intermediates (**534–537**), which, without isolation, were desilylated with $n$$Bu_4NF$ to form 2′-deoxy-3′-keto-*C*-nucleosides (**538–541)**. Stereospecific reduction of (**538–541**) and removal of the *p*NPE protecting group of **546** and **547** resulted in the target compounds (**542–545)** (Scheme 93).

Seitz and Singh diastereoselectively synthesized β-aryl-*C*-2-deoxynucleosides from furanoid glycal derived glycal epoxides.[74] The glycal **66f** on treatment with DMDO in DCM at 0 °C was converted to epoxide **548**. Its reaction with trinaphthylaluminum **549** yielded 1-naphthyl-β-*C*-arabinonucleoside **550** by *cis* opening of the epoxide ring. It was transformed into methyl xanthate **553** *via* phenylthionocarbonate **551** and thiocarbonylimidazole **552**. They failed to reduce **553** to **554** by treatment with $n$$Bu_3SnH$ or $(TMS)_3SiH$ in presence of AIBN due to the bulkiness of the two TBDPS groups (Scheme 94).

Then they selected TBDMS-protected glycal **66e.**[23] The required epoxide **555** was obtained from the known glycal **66e** by treating it with dimethyldioxirane (DMDO). The *cis* opening of epoxide **555** was performed by treatment with trinaphthylaluminum to afford 1-naphthyl-β-*C*-arabinonucleoside **556a** (method 1) in 50% yield from **66e.** The nucleoside **556a** was allowed to react with thiocarbonyldiimidazole to form **557a,** which on reduction with $(TMS)_3SiH$ and AIBN furnished 2′-deoxynucleoside **558a** in 82% yield. Finally, the silyl ether deprotection was performed by treatment with $n$$Bu_4NF$ in THF to afford fully deprotected 2′-deoxy-1′-β-naphthyl nucleoside



Scheme 94



Scheme 95

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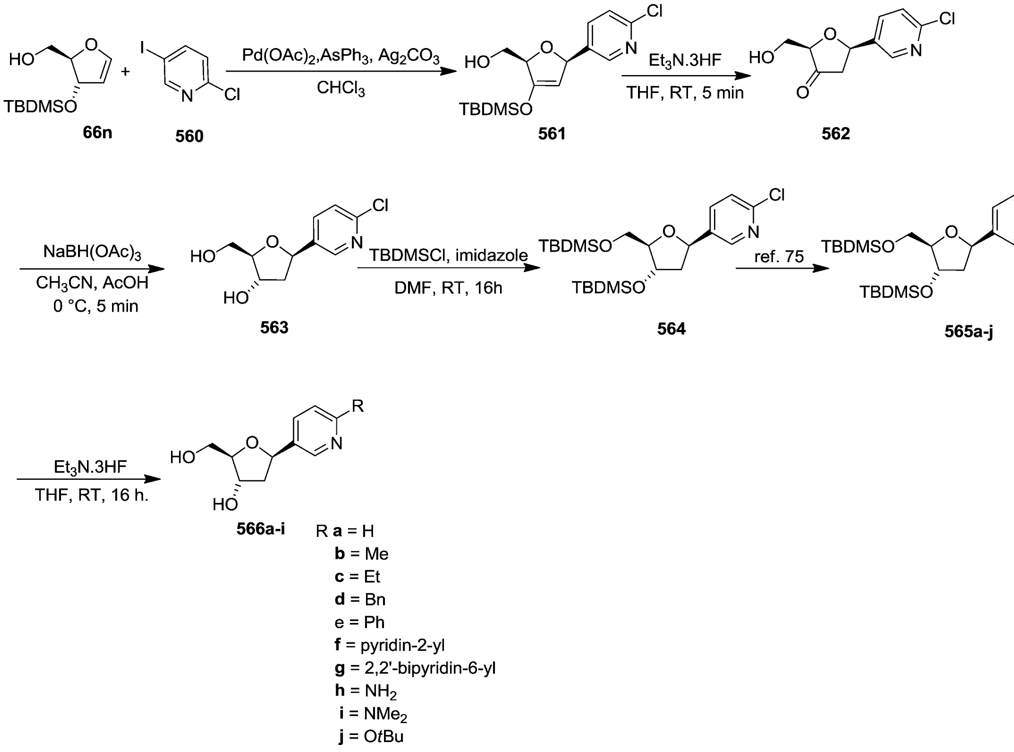
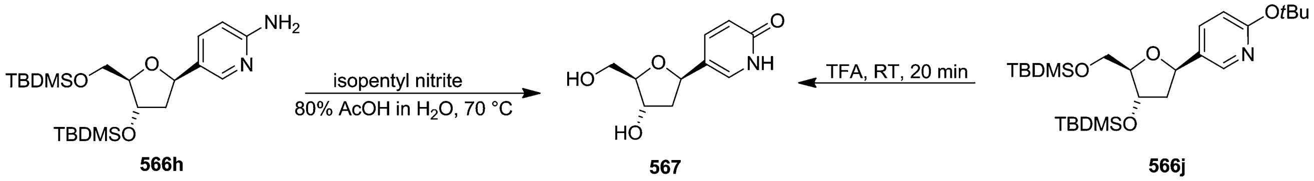


Scheme 96



Scheme 97

559a in 98% yield. They further studied the reaction sequence by changing triarylaluminum reagent for *cis* opening of the glycal epoxide to dimethylarylaluminum reagent (method 2). They synthesized a series of 2′-deoxy-1′-β-naphthyl nucleoside **559a–d** by employing both the two methods (Scheme 95).

In 2007, Hocek and co-worker have developed a novel methodology for the synthesis of 6-substituted pyridin-3-yl *C*-nucleosides.[75] After several trial experiments, they optimized the Heck reaction of 2-chloro-5-iodopyridine **560** with glycal **66n** in the presence of $Pd(OAc)_2/AsPh_3$ and Ag_2CO_3 in chloroform to give the desired *C*-nucleoside precursor **561** in acceptable 65% yield. Desilylation followed by reduction of the corresponding keto **562** with $NaBH(OAc)_3$ in a mixture of acetonitrile and acetic acid afforded **563** in a good yield of 70% for the two steps. The free hydroxyl group of nucleoside **563** was then protected with TBDMSCl with imidazole in DMF to afford the fully protected key intermediate β-*C*-nucleoside **564** in 87% yield (39% overall yield over four steps from glycal **66n**), (Scheme 96). They prepared 6-unsubstituted pyridine nucleoside **565a** by catalytic hydrogenation of **564** with H_2 over Pd/C for 3 h, in a mixture of EtOH, THF, and H_2O, in presence of Et_3N. This key intermediate **564** was then subjected to a series of palladium catalyzed cross-coupling reactions to form new pyridine *C*-nucleosides **565b–g** bearing diverse C (6-alkyl, 6-aryl, or 6-hetaryl) groups. They performed Hartwig-Buchwald aminations, and alkoxylations on **564** to give a series of protected 1β-(6-amino-, and 6-*tert*-butoxypyridin-3-yl)-2′-deoxyribonucleosides **565h–j** in good yields. All the silylated nucleosides **565a–i** were deprotected using $Et_3N\cdot 3HF$ in THF to give the free 6-substituted pyridine *C*-nucleosides **566a–i** in good yields (Scheme 96).

6-Oxopyridine *C*-nucleoside **567** was synthesized in 84% yield by this research group from 6-(*tert*-butoxy)pyridine derivative **566j** on treatment with TFA for 20 min. They also synthesized *C*-nucleoside **567** from aminopyridine *C*-nucleoside **566h** by reacting it with isopentyl nitrite in 80% aqueous AcOH at 70 °C for 100 min. However, here **567** was isolated along with some inseparable impurities (Scheme 97).[75]

6. Synthesis of *N*-nucleosides

In 1990 Danishefsky and Chow proposed the epoxidation of furanoid glycals and showed their application towards the

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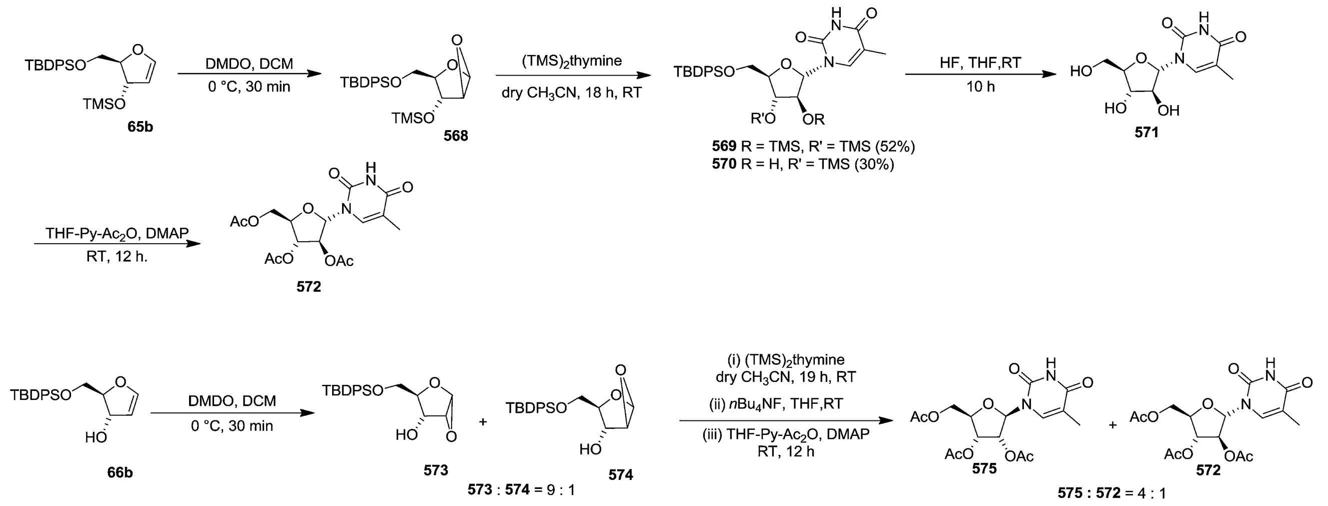
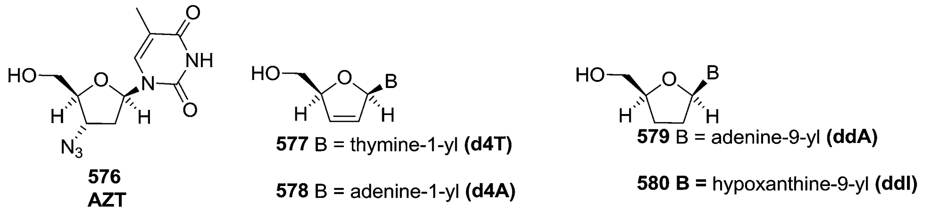
synthesis of nucleosides.[8] The epoxidation of furanoid glycal **65b** with DMDO (dimethyldioxirane) was highly face selective to give **568.** The treatment of the epoxide **568** with $(TMS)_2$thymine provided a mixture of **569** (52% yield) and **570** (30% yield). The mixture was deprotected with TBAF in THF to afford **571.** Its acetylation with Ac_2O-DMAP afforded C1-*epi*-arabinonucleoside triacetate **572** in 94% yield. On the other hand, reaction of furanoid glycal **66b** (having free hydroxyl group at C-3) with DMDO in acetone with a minimal amount of DCM afforded 1 : 1 mixture of anhydro sugars **573** and **574.** They further investigated reaction of **66b** with a mixture of acetone/DCM in 6 : 1 ratio to furnish mixture of epoxides **573** and **574** in 9 : 1 ratio. Treatment of the mixture with $(TMS)_2$thymine in acetonitrile followed by desilylation with TBAF in THF and acetylation with acetic anhydride/DMAP resulted in a mixture of **575** and **572** in 4 : 1 ratio with 36% yield (Scheme 98).

In 1991 Kim *et al.* prepared phosphonate isosteres of **577** (d4T), **578** (d4A), and **579** (ddA) (Fig. 5) monophosphates using regiospecific and highly stereoselective electrophilic addition to furanoid glycals as the key step.[76] The starting material for this study was the glycal **582,** which was readily prepared from thymidine **64a** *via* thymidine-5′-carboxylic acid **581** in two steps by adopting the reported procedure of Horwitz and coworkers.[77] Glycal **582** was treated with PhSeCl at −70 °C, to give a 12 : 1 mixture of **583** and **584** in high yield. This mixture was allowed to react with silver perchlorate in the presence of dimethyl(hydroxymethyl)phosphonate to afford the phosphonate **585** in 41% overall yield. It was then transformed into the d4T phosphonate analogue **587** by the sequential oxidation with sodium periodate in methanol followed by phosphonate ester removal of the resulting **586** with TMSBr in DMF and finally by neutralization with $NaHCO_3$ in overall 52% yield (Scheme 99). They also showed phosphonates **586** exhibited a potent antiviral activity comparable to that of **577** (d4T).

They also described the synthesis of glycal **591** from 2′-deoxyadenosine **588** by following the same reaction sequence described for glycal **582.** Glycal **591** on treatment with dimethyl(hydroxymethyl)phosphonate in the presence of *N*-(phenylseleno)phthalimide or IBr afforded **592** (65% yield) or **593** (95% yield) in a regiospecific and a highly stereoselective manner. Oxidative elimination of the phenylselenyl group in **592** or base (DBU) promoted elimination of hydrogen iodide in **593** gave olefin **594** in high yield, which on deprotection was converted to **595,** phosphonate isostere of d4A (**578**) monophosphate, by following the same reaction sequence for the conversion of **586** to **587.** The tetrahydrofuranyl derivative **596,** a phosphonate isostere of ddA (**579**) monophosphate was also prepared by catalytic hydrogenation of the olefin **595.** Dihydroxylation of the double bond in **594** with catalytic OsO_4 and NMO as the oxidant gave diol **597** as a single isomer in high yield. The deblocking of the protecting groups in **597** led to **598,** which is a phosphonate isostere of adenosine monophosphate. These d4T and d4A phosphonate analogues **587** and **595** exhibited potent anti HIV activity (Scheme 100).



Scheme 98



576
AZT

577 B = thymine-1-yl **(d4T)**

578 B = adenine-1-yl **(d4A)**

579 B = adenine-9-yl **(ddA)**

580 B = hypoxanthine-9-yl **(ddI)**

Fig. 5 Structures of AZT **576**, d4T **577**, d4A **578**, ddA **579** and ddI **580**.

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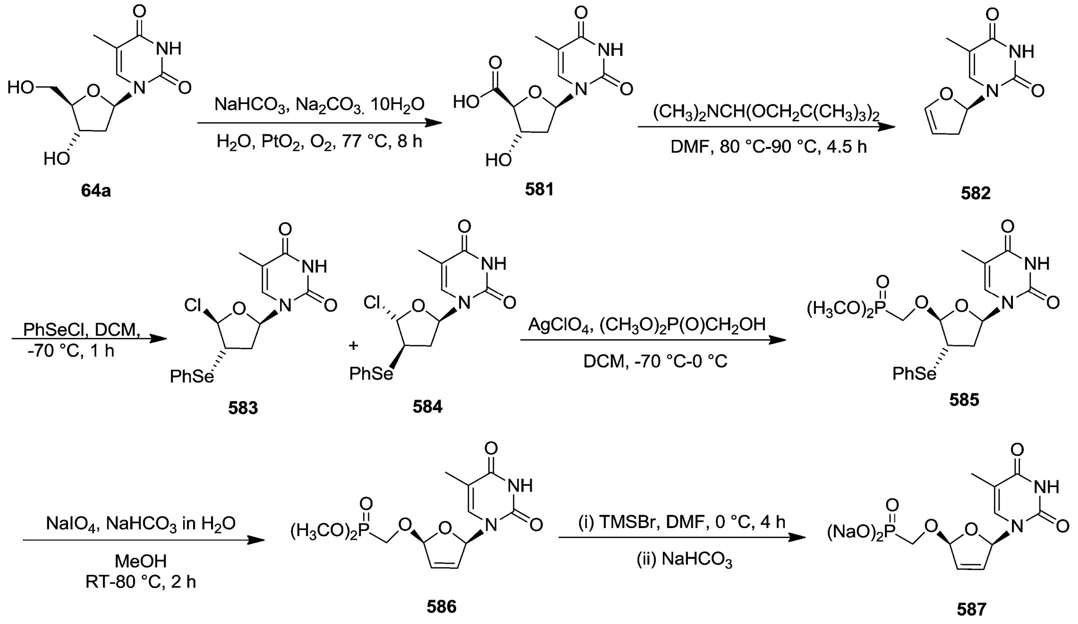
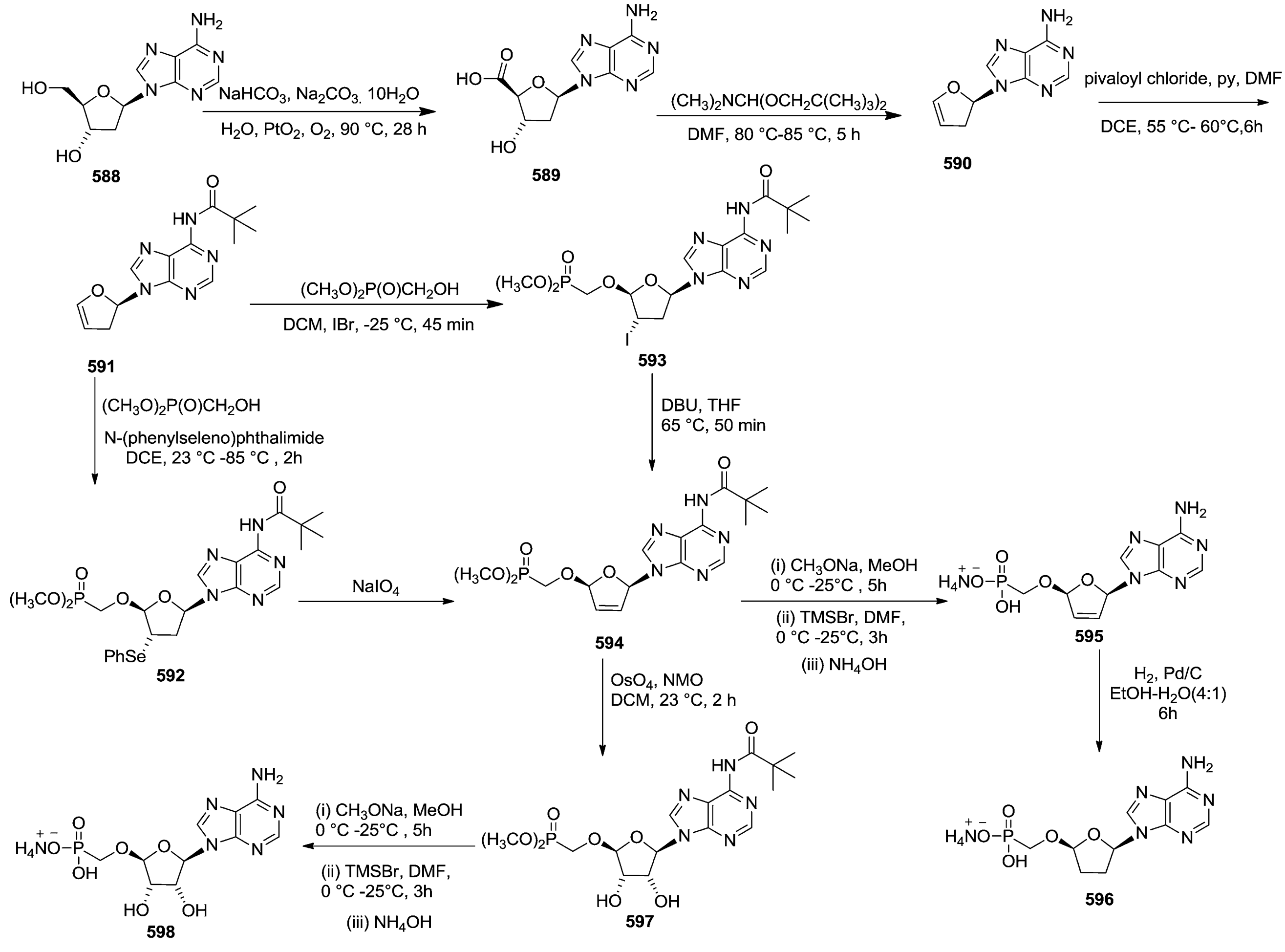


Scheme 99



Scheme 100

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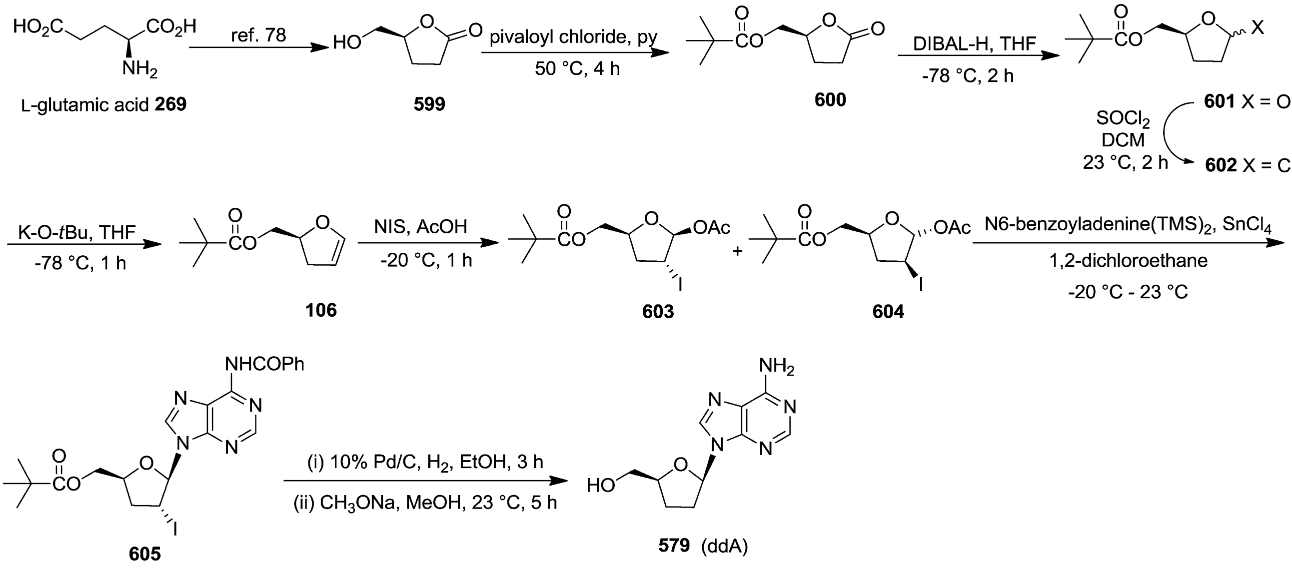
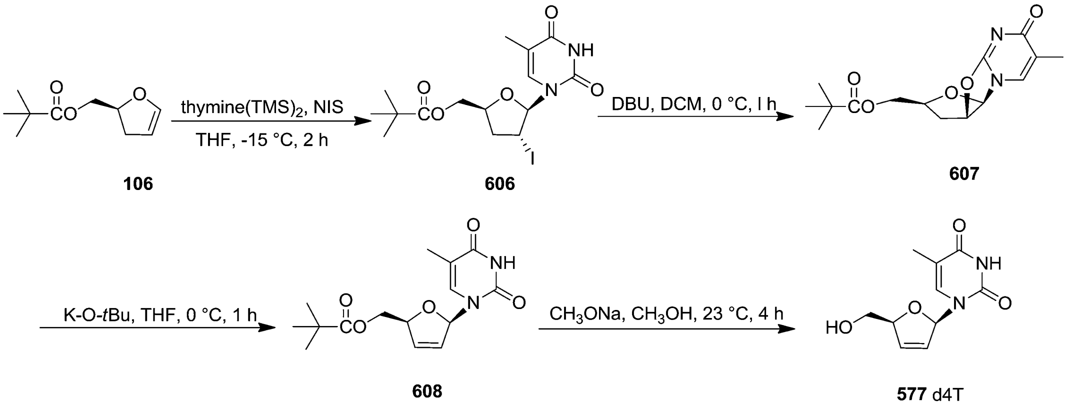
In 1992, Kim and Misco, demonstrated highly stereoselective synthesis of d4T **577** and ddA **579**, antiviral nucleosides, from L-glutamic acid **269** *via* furanoid glycal intermediate.[9] The synthesis of the requisite furanoid glycal **106** was derived from the known lactone **599** which was in turn, readily available by the diazotation-lactonization of L-glutamic acid **269**.[78] Pivaloyl group protection of the free hydroxyl group of **599** with pivaloyl chloride gave **600**, which on DIBALH reduction afforded **601**. Its chlorination with $SOCl_2$ followed by elimination of chloride **602** with KO*t*Bu gave the glycal **106** (overall 52% yield). Addition of acetic acid to glycal **106** in the presence of NIS produced a mixture of **603** and **604** in a ratio of 14 : 1. This mixture without further purification was coupled with silylated N6-benzoyladenine in the presence of $SnCl_4$ to give the adenosine analogue **605** (45% yield over 2 steps) after chromatographic purification. Hydrogenolysis of iodide **605** followed by removal of the pivaloyl group by saponification gave ddA **579** in 75% yield (Scheme 101).

Then they repeated this reaction sequences with pyrimidine series. But in this case, they directly coupled the pyrimidine base and the furanoid glycal in the presence of NIS. When NIS was added to a mixture of glycal **106** and silylated thymine in DCM, the desired thymidine analogue **606** was formed as a major product (Scheme 102), which without purification, on treatment with DBU furnished the anhydro intermediate **607** in 52% overall yield. Its treatment with KO*t*Bu in THF produced olefin **608** (82% yield) which on acyl deprotection with NaOMe yielded **577** (d4T) in 95% yield.

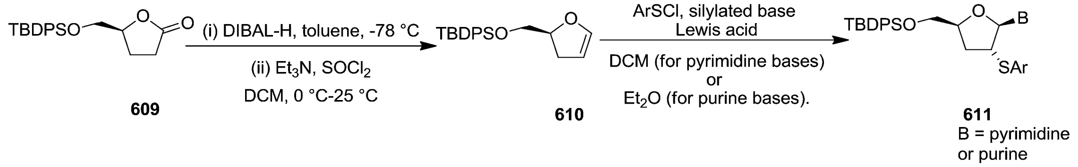
Liotta *et al.* described the synthesis of nucleosides *via* region- and stereoselective electrophilic addition to furanoid glycals **610** which was prepared from lactone **609** in a straightforward fashion.[79] The DIBAL-H reduction of **609** followed by addition of $SOCl_2$ and Et_3N to the corresponding lactol afforded furanoid glycal **610**. Its exposure to an appropriate source of electrophilic sulfur in the presence of a silylated nucleoside base and Lewis acids produced the pyrimidine and purine derivatives **611** in



Scheme 101



Scheme 102



Scheme 103

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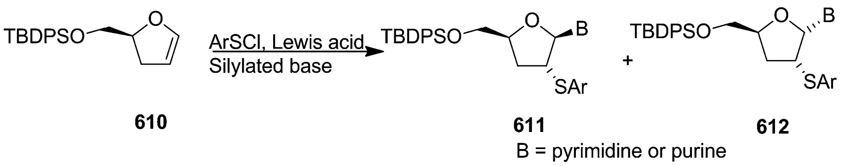
Table 11 Additions of arylsulfenyl chlorides/silylated bases to glycals

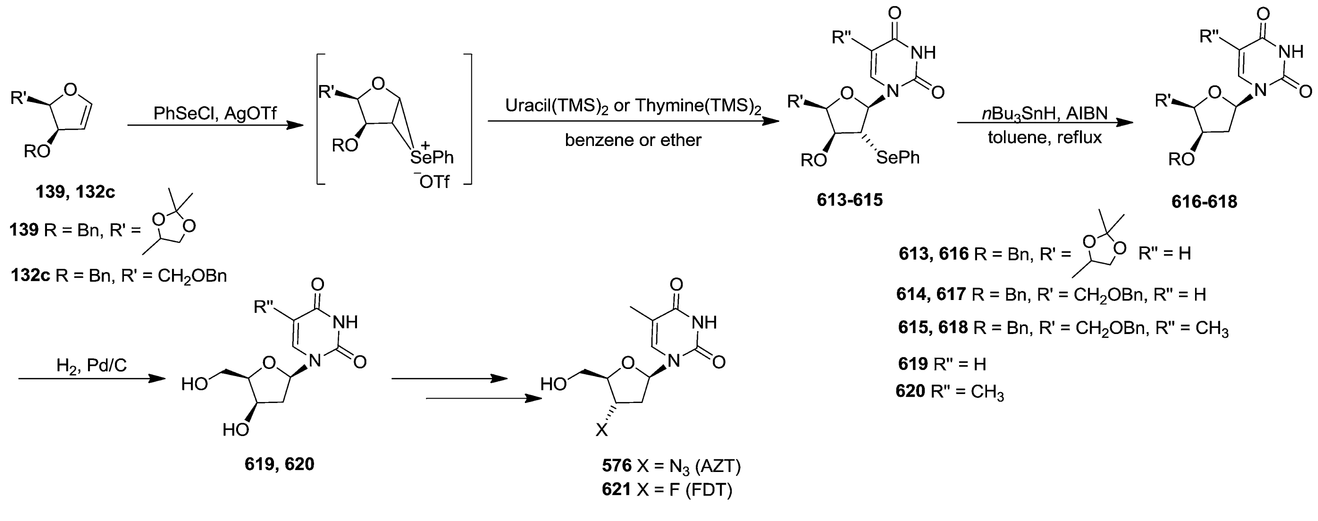


Entry	ArSCl	Lewis acid[a]	Silylated base	Conditions[b] (°C)	Ratio (β : α)	Time (h)	Yield (%)
1	PhSCl	$SnCl_4$	*N*-Ac-Cytosine	−78 to 25	18 : 1	2	65
2	PhSCl	TMSOTf	*N*-Ac-Cytosine	−78 to 0 to 25	5 : 1	1.5	60
3	TIPPSCl	$SnCl_4$	*N*-Ac-Cytosine	−78 to 25	23 : 1	2	70
4	TIPPSCl	TMSOTf	*N*-Ac-Cytosine	−78 to 0 to 25	6 : 1	2	73
5	PhSCl	$SnCl_4$	Thymine	−78 to 25	42 : 1	2	68
6	PhSCl	TMSOTf	Thymine	−78 to 0 to 25	4 : 1	2	50
7	TIPPSCl	$SnCl_4$	Thymine	−78 to 25	44 : 1	2	60
8	TIPPSCl	$SnCl_4$	Uracil	−78 to 25	>99 : 1	2	52
9	TIPPSCl	TMSOTf	6-Cl-Purine	−78 to 25	5 : 1	5	80

[a] The reaction utilized 1 .15 eq. of Lewis acid. [b] (i)−78 to 0 to 25 °C: after addition of the sulfenyl chloride, the reaction was kept at −78 °C for 30 min and then warmed to 0 °C. The silylated base and Lewis acid were then introduced, and the reaction was allowed to warm to room temperature (25 °C). (ii) −78 to 25 °C: after addition of the sulfenyl chloride, the reaction was kept at −78 °C for 30 min. The silylated base and Lewis acid were then introduced and the reaction was allowed to warm to room temperature. (iii) The solvent of choice for pyrimidine bases was DCM and diethyl ether for purine bases. TIPP = 2,4,6-triisopropylphenyl.

a stereo- and regioselective fashion by judicious choice of the Lewis acid, solvent and temperature (Scheme 103, Table 11).

In 1993, Castillón and co workers showed selenium controlled stereoselective synthesis of a series of 2′-deoxy nucleosides and a formal synthesis of 3′-azido-3′-deoxythymidine (AZT, **576**) and 3′-fluoro-3′-deoxythymidine (FDT, **621**), a powerful anti HIV agent, starting from furanoid glycals. Furanoid glycals **139** and **132c** were derived from 2,3:5,6-di-*O*-



Scheme 104

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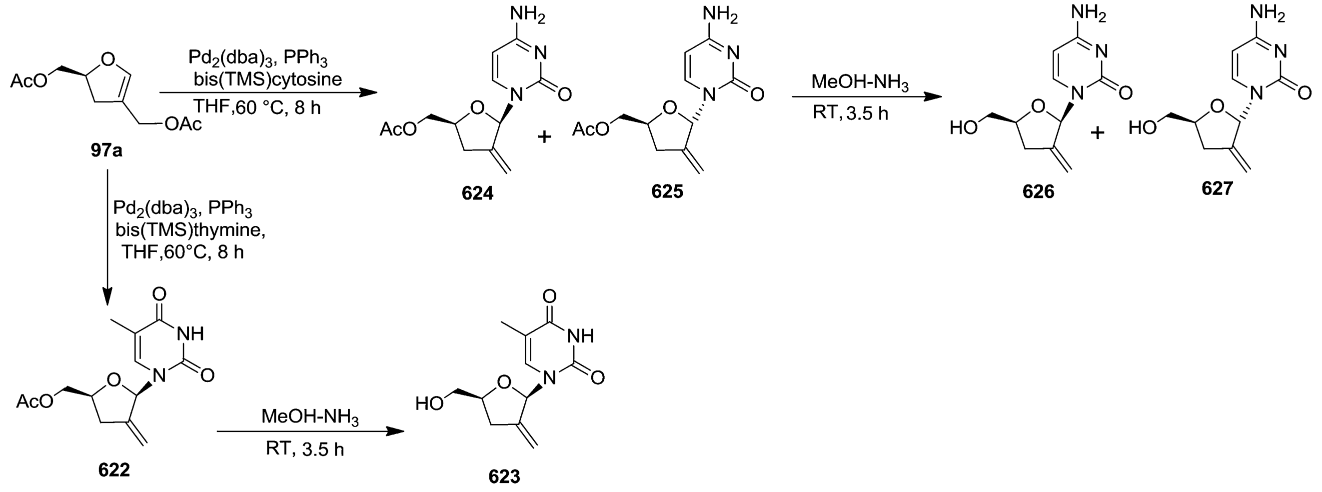
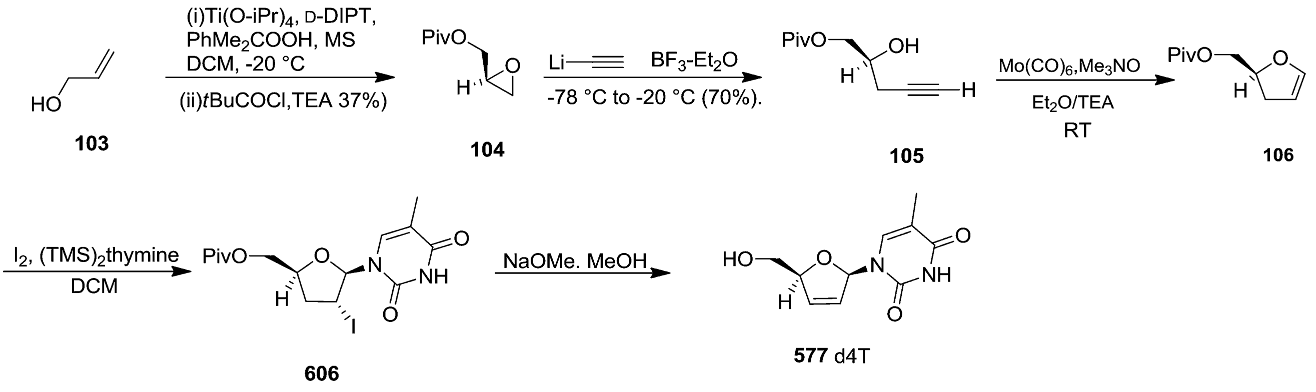


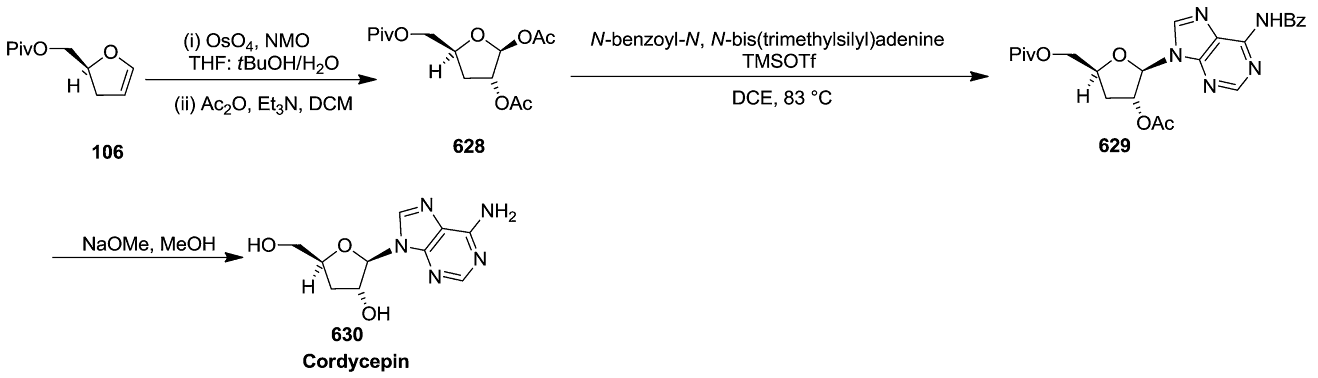
Scheme 105



Scheme 106

isopropyliden-*manno* furanose[31] and 2,3-*O*-isopropylidene-*lyxo*-furanose[30] respectively.[10] These glycals (**139** and **132c**) on treatment with PhSeCl in presence of AgOTf followed by glycosylation with pyrimidine bases in non polar solvents accomplished 2′-deoxy-2′-phenylselenenyl nucleosides **613–615**. In all cases, removal of the phenylselenenyl group was carried out by reaction with nBu$_3$SnH in refluxing toluene to afford 2′-deoxynucleosides **616–618** in 80–90% overall yields from the glycal. Hydrogenolysis of compounds **617** and **618** using Pd/C as the catalyst gave the unprotected nucleosides **619** and **620** in quantitative yield (Scheme 104).

In 1995, Florent and coworkers also showed the utilization of furanoid glycal **97a** (synthesized from α-D-isosaccharino-1,4-lactone **93**, Scheme 16) for the synthesis of 2′,3′-dideoxy-2′-*C*-methylidene-5-methyl uridine **623**, 3′-deoxy analog of DMDC **626** and **627**.[27] The glycosylation of bis-(trimethylsilyl)thymine



Scheme 107

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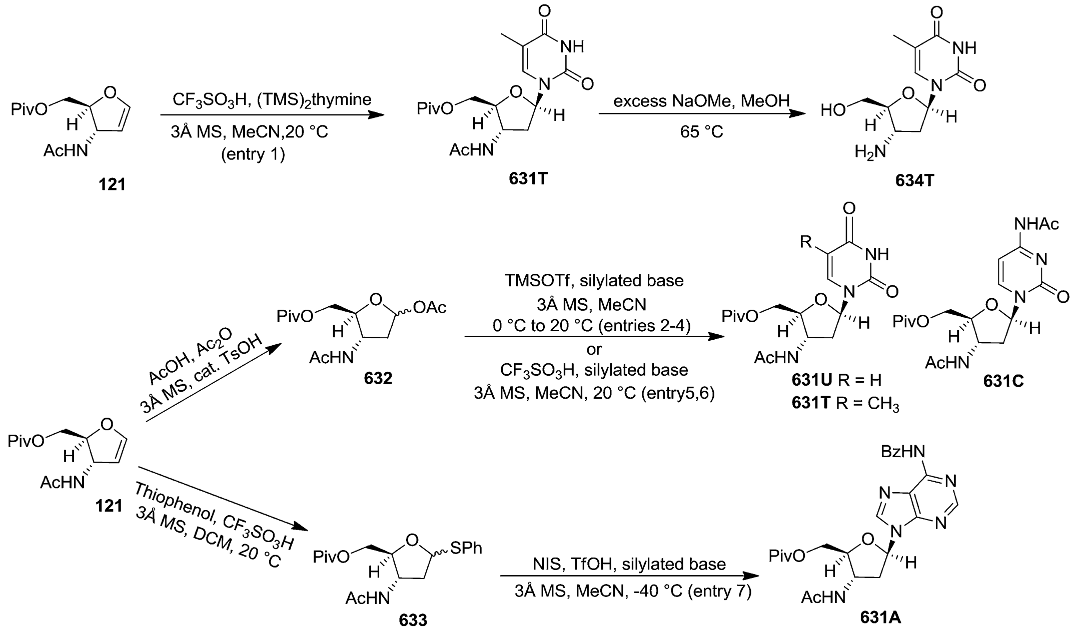

Scheme 108

with crude furanoid glycal in the presence of $Pd_2(dba)_3$ and PPh_3 gave nucleoside **622** in 25% overall yield. Deprotection by ammonolysis led to the 2′,3′-dideoxy-2′-*C*-methylidene-5-methyl uridine **623** (80% yield). Glycosylation of silylated cytosine with **97a** under the identical reaction conditions afforded β-nucleoside **624** along with the corresponding α-anomer **625** (40% overall yield and ratio $\beta : \alpha = 8 : 2$) after column purification of the crude product mixture. Removal of the acetyl group produced 3′-deoxy analog of DMDC **626** and **627** (Scheme 105).

McDonald and coworkers synthesized Stavudine (d4T, **577**), an anti-AIDS compound,[80] from allyl alcohol **103** derived furanoid glycal key intermediate **106**, whose synthesis already described in Scheme 18.[29,80] Iodine-mediated addition of $(TMS)_2$thymine to **106** gave iodonucleoside **606** which on without further purification treated with freshly prepared NaOMe to accomplish stavudine **577** (d4T) (Scheme 106).

Dihydroxylation of **106** with OsO_4 in presence of NMO followed by acylation of the crude diol provided a 13 : 4 : 3 : 1 mixture of diacetylated products favouring **628** (Scheme 107). This mixture was subjected to Lewis acid catalyzed adenine glycosylation to give a 9 : 1 mixture of stereoisomers favouring **629**. Methanolysis of acyl groups followed by column purification produced the synthetic cordycepin **630** (Scheme 107).

After reporting the synthesis of d4T **577** and cordycepin **630** from **106**, McDonald and Gleason then optimized the glycosylation of 3-amidofuranose glycal **121** or **122** (whose synthesis already discussed in Scheme 19, Table 4) with pyrimidine and purine bases and found that reaction of **121** with CF_3SO_3H and silylated thymine at room temperature with acetonitrile as solvent afforded predominantly the β-nucleoside **631T** (Scheme 108, Table 12, entry 1).[29] Treatment of **121** with acetic acid gave a more highly reactive glycosyl donor **632**, which underwent high-yielding TMSOTf-induced glycosylation with silylated pyrimidine bases in the presence of acetonitrile to afford the desired β-nucleoside **631T**, **U**, **C** (Table 12, entries 2–4). They obtained similar results by using CF_3SO_3H as the activating agent (Table 12, entries 5 and 6); possibly CF_3SO_3H was also generated by *in situ* hydrolysis of trimethylsilyl trifluoromethanesulfonate.

For the addition of purine bases, they treated the more reactive thioglycoside donor **633** obtained from **121** with NIS and CF_3SO_3H at significantly lower temperature giving the purine β-nucleoside **631A** with high stereoselectivity (Table 12, entry 7). The deblocking of ester and amide protective groups of **631T** with NaOMe in MeOH gave the 3′-amino-2′,3′-dideoxythymidine **634T**.

In the case of guanine glycosylations, the reaction of **633** under kinetic conditions gave primarily the N-7 regioisomer **631G*** as the major nucleoside product (Scheme 109, Table 13,

Table 12 Glycosylation of **121** to 3′-amido-2′,3′-dideoxynucleosides[a]

Entry	Silylated base	Glycosyl donar	Conditions	Nucleoside, isolated yield (β : α ratio)
1	$(TMS)_2$-thymine	**121**	a	**631T**, 50% (>20 : 1)
2	$(TMS)_2$-thymine	**632**	b	**631T**, 85% (4.7 : 1)
3	$(TMS)_2$-uracil	**632**	b	**631U**, 85% (21 : 1)
4	*N*-Ac$(TMS)_2$-cytosine	**632**	b	**631C**, 77% (8.7 : 1)
5	$(TMS)_2$-thymine	**632**	c	**631T**, 87% (8.4 : 1)
6	*N*-Ac$(TMS)_2$-cytosine	**632**	c	**631C**, 84% (3.3 : 1)
7	*N*-Bz$(TMS)_2$-adenine	**633**	d	**631A**, 42% (>10 : 1)

[a] (Method a) CF_3SO_3H, silylated base, 3 Å MS, MeCN, 20 °C (entry 1); (Method b) TMSOTf, silylated base, 3 Å MS, MeCN, 0 °C to 20 °C (entries 2–4); (Method c) CF_3SO_3H, silylated base, 3 Å MS, MeCN, 20 °C (entries 5, 6); (Method d) NIS, TfOH, silylated base, 3 Å MS, MeCN, −40 °C (entry 7).

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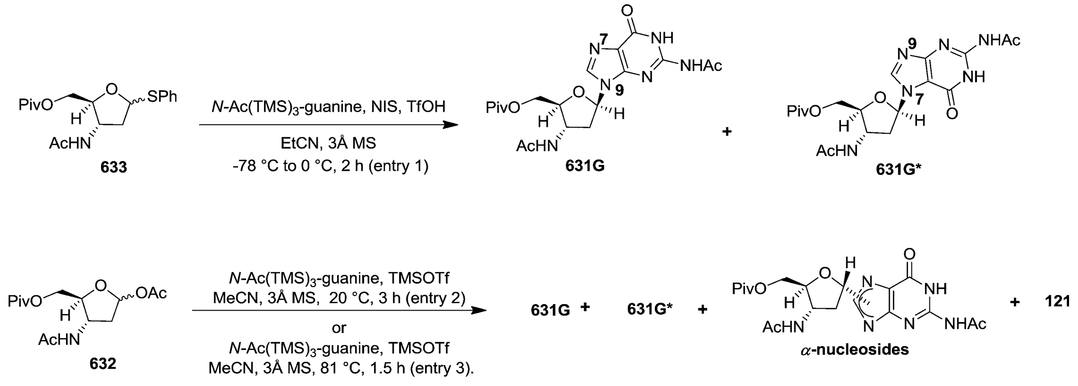


Scheme 109

Table 13 Glycosylation of **632** and **633** with silylated guanine base[a]

Entry	Glycosyl donar	Condition	Nucleosides, combined yield	Relative ratio of products **631G** : **631G*** : α-nucleosides : **121**
1	**633**	a	35%	1.0 : 7.3 : 0 : 0
2	**632**	b	38%	3.4 : 1.4 : 1.0 : 0
3	**632**	c	50%	2.2 : 1.0 : 12 : 3.2

[a] (Method a) N–Ac(TMS)$_3$-guanine, NIS, TfOH, EtCN, 3 Å MS, −78 °C to 0 °C, 2 h (entry 1); (Method b) N–Ac(TMS)$_3$-guanine, TMSOTf, MeCN, 3 Å MS, 20 °C, 3 h (entry 2); (Method c) N–Ac(TMS)$_3$-guanine, TMSOTf, MeCN, 3 Å MS, 81 °C, 1.5 h (entry 3).

entry 1). They observed that when glycosylation of guanine with **632** was carried out at room temperature, the proportion of N-9 regioisomer **631G** increased along with α-nucleoside isomers (entry 2) and were the major product when the glycosylation was conducted in refluxing acetonitrile (entry 3).

Epoxidation of **121** with peroxyacids gave **635** (Scheme 110). Acylation of free hydroxyl group yielded **636** which permitted *trans*-glycosylation under Lewis acid conditions to give purine β-nucleosides including **637**. Basic methanolysis of **637** yielded the deprotected puromycin aminonucleoside **638.**

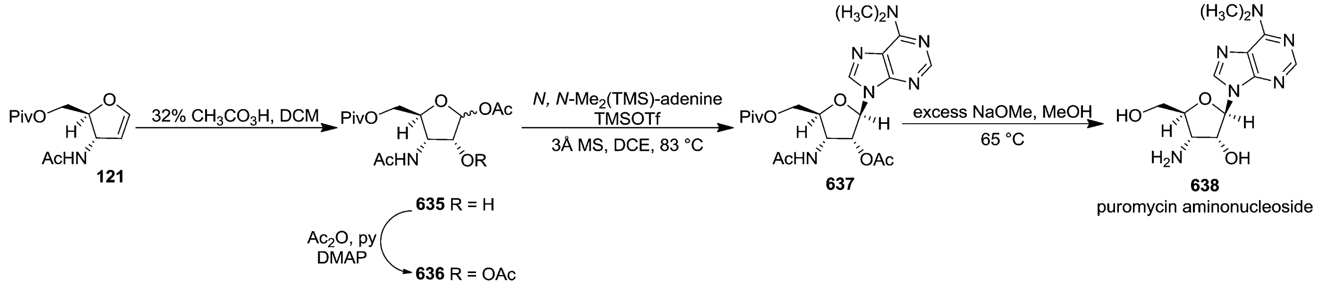
Peroxyacetic acid epoxidation followed by acetylation of 3-trifluoroacetamide glycal **122** furnished diacetate **640** *via* **639** (Scheme 111). Under the thermodynamic conditions of these glycosylations, the naturally occurring N-9 regioisomers **641A**, **641G**, and **641A′** were the major products (Table 14, entries 1–3).

DMDO epoxidation of **122** was also directed by the amide when epoxidation was conducted in solvent DCM. The crude glycal epoxide **642** reacted stereospecifically with silylated pyrimidine bases to give **641T**, **U**, **C** in good yields (Scheme 111, Table 14, entries 4–6), whereas in the case of pyrimidine bases, benzoyladenine gave **641A** in a very low isolated yield (Table 14, entry 7).

In 1997, Castillón *et al.* also reported the formation of 2′,3′-dideoxy nucleosides by electrophilic addition of selenium to furanoid glycal **610**, which was synthesized from 2-deoxyribose **67**.[81] They further discussed the synthesis of d4T **577** *via* precursor **656** through selenium-mediated glycosylation and selenoxide elimination.

Thus, 2-deoxyribose **67** was converted into the phenyl-1-seleno-glycoside **645** (mixture α/β = 1.9 : 1) in four steps involving methyl glycoside synthesis, selective 5-OH protection, Barton deoxygenation, and treatment with PhSeH in the presence of $BF_3 \cdot OEt_2$. Oxidation of **645** gave glycal **610** with a yield of 52%. The reaction of glycal **610** with $(TMS)_2$uracil, PhSeCl, and AgOTf at room temperature in ether led to a mixture of 2′-phenylselenenyl nucleosides **648** and **649** in a 99 : 1 ratio in good yield. Similarly, they treated glycal **610** with $(TMS)_2$-thymine to obtain 2′-phenylselenenyl nucleosides **650** and **651** with a ratio of 90 : 10 in excellent yields.

Under identical reaction condition, the reaction of glycal **610** with silylated 6-chloropurine showed a lower stereoselectivity (ratio **652**/**653**, 3 : 1). In order to increase the β-stereoselectivity of the glycosylation step, they synthesized glycal **647** in a similar way the glycal **610** was synthesised. In this case a mixture of **654**/**655** (β/α = 89 : 11) was obtained in a yield of 78% (Scheme 112).



Scheme 110

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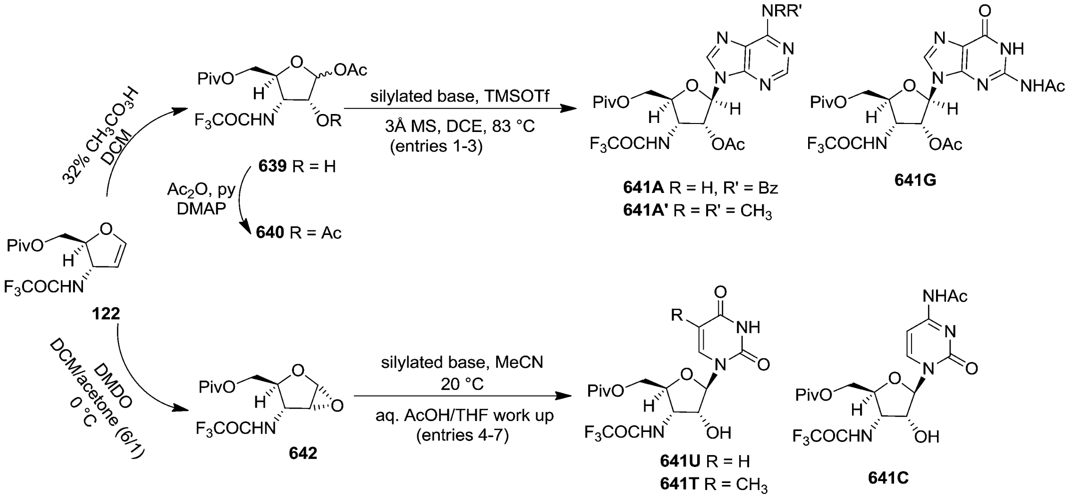


Scheme 111

Table 14 Epoxidation/glycosylation of **122** to 3′-amido-3′-deoxynucleosides[a]

Entry	Silylated base	Glycosyl donar	Conditions	Nucleoside, isolated yield
1	*N*-Bz(TMS)$_2$-adenine	**640**	a	**641A**, 90%
2	*N*-Ac(TMS)$_3$-guanine	**640**	a	**641G**, 77% (10 : 1)
3	*N*,*N*–Me$_2$(TMS)-adenine	**640**	a	**641A′**, 71%
4	(TMS)$_2$-uracil	**642**	b	**641U**, 80%
5	(TMS)$_2$-thymine	**642**	b	**641T**, 86%
6	*N*-Ac(TMS)$_2$-cytosine	**642**	b	**641C**, 71%
7	*N*-Bz(TMS)$_2$-adenine	**642**	b	**641A**, 16%

[a] (a) silylated base, TMSOTf, 3 Å MS, DCE, 83 °C, (entries 1–3); (b) silylated base, MeCN, 20 °C, aq. AcOH/THF work up (entries 4–7).

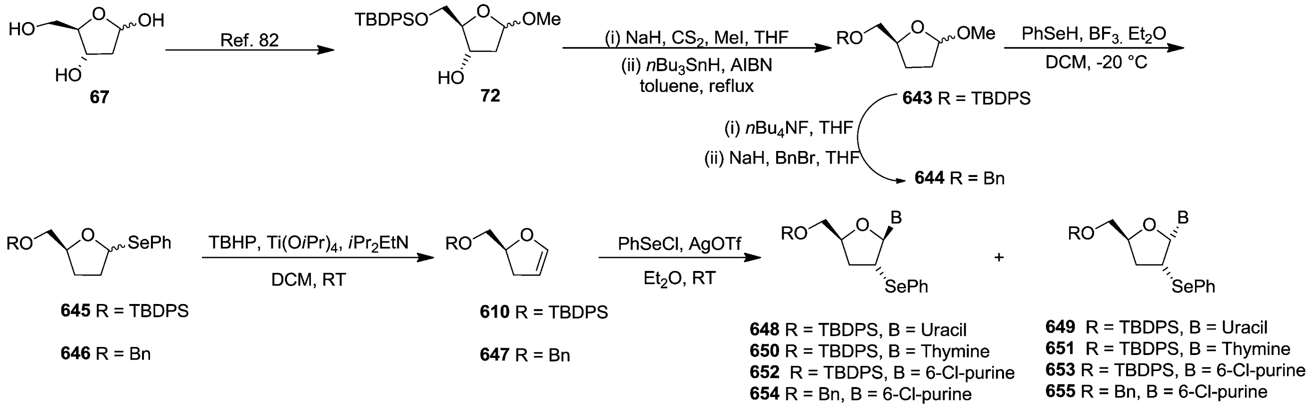
Compound **650** on oxidative elimination afforded the corresponding didehydro derivative **656** in 85% yield by using *t*BuOOH/Ti(O^{i}Pr)$_4$ as an oxidative system; the deprotection of the TBDPS group gave d4T **577** (Scheme 113).

In the same year, this group also reported stereoselective synthesis of 2′-deoxy-2′-phenylselenenyl nucleosides from furanoid glycals in a "one pot" reaction and efficiently converted them into 2′-deoxy nucleosides.[83] They also showed the stereoselectivity of the reaction was affected by some of the factors such as stereochemistry at position 3, the nature of the protecting groups, the phenylselenenyl reagent and the solvent. For this purpose they synthesized a series of furanoid glycals. Glycal **139** and **214** (ref. 5) from D-mannose derived furanoid glycal **26.** The glycal **132c** was prepared from D-mannose by degradation of the side chain, in a similar way to **26,**[21] or from 2-deoxyribose **67.**[24]

Treatment of **139** with PhSeCl and (TMS)$_2$uracil in the presence of AgOTf in ether at room temperature yielded β-gluco nucleoside **613** and α-gluco nucleoside **657** in 81% yield (ratio **613**/**657** = 90 : 10) (Scheme 114, Table 15, entry 1).

Under the identical reaction condition treatment of glycal **214** and **132c** afforded 2′-deoxy-2′-phenylselenenyl nucleosides β-gluco **658**/α-gluco **659** (86 : 14) in 95% yield and β-xylo **614**/α-xylo **660** (91 : 9) in 91% yield respectively (Table 15, entries 2 and 3).

To show the stereoselectivity in the formation of 2′-deoxy-2′-phenylselenenyl nucleosides derived from *erythro* configured furanoid glycals, they synthesized glycals **661, 662, 66e** and **665** (Table 16) from D-ribonic-γ-lactone[18] and **71a, 90, 663, 664** and **66j** from 2-deoxyribose.[24,28] For the glycals (**661, 662, 66e, 71a,**



Scheme 112

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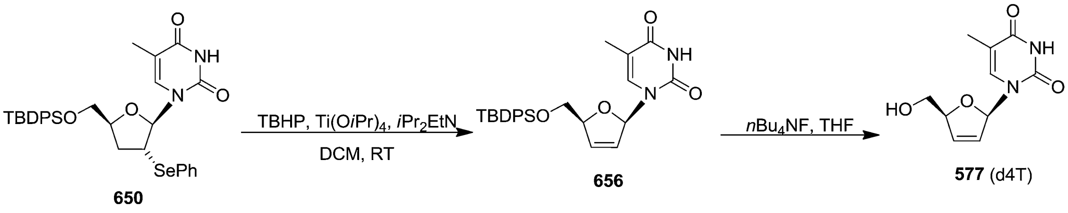
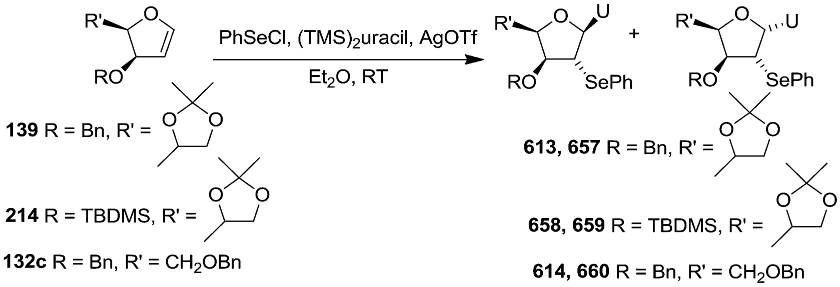
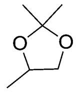
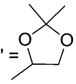


Scheme 113



Scheme 114

Table 15 Stereoselectivity in the synthesis of 2′-phenylselenenyl nucleosides derived from *threo* glycals[a]

	Starting glycals	Time (h)	Yield[b] (%)	2′-Selenenyl nucleosides[c] (diastereomeric ratio)
139	R = Bn, R′ = 	1	81	β-Gluco **613** : α-Gluco **657** (90 : 10)
214	R = TBDMS, R′ = 	1	95	β-Gluco **658** : α-Gluco **659** (86 : 14)
132c	R = Bn, R′ = BnOCH$_2$	0.5	90	β-xylo **614** : α-xylo **660** (91 : 9)

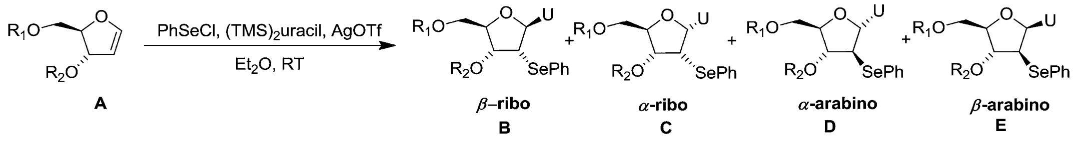
[a] Reactions were carried out using the molar ratio glycal/PhSeCl/AgOTf/Uracil(TMS)$_2$ = 1/1.5/1.7/2. [b] Expressed as a percentage of recovered mixture of products after chromatography. [c] Determined by integration of the H-1′ protons in the ^{1}H NMR spectrum of the reaction mixture.

90, **663**, **664**, **665** and **66j**) with an *erythro* configuration, stereoselectivity was seen to depend on the protecting groups at positions 3 and 5 (Scheme 115, Table 16).

They further synthesized 2′-deoxy nucleosides from 2′-deoxy-2′-phenylselenenyl nucleosides *viz.* β-gluco nucleoside **613**, β-xylo **614**, and α-arabino **669** and β-ribo **672** by their treatment with *n*Bu$_3$SnH and AIBN in refluxing benzene to give 2′-deoxy nucleosides **616**, **617** and **675**, **676** respectively (Scheme 116).

In 1997, Robles and coworkers have shown synthesis of a series of 2′-deoxy-2′-iodo nucleosides (**678–684**), from furanoid glycals (**133c**, **76b**, **132c** and **136c**), which were synthesized from differently *O*-protected D-xylo **133a**, **677**, **132a** and D-gluco **136a** configured furanoid 1,2-diols respectively on treatment with I$_2$/PPh$_3$/imidazole. NIS-mediated glycosylation of furanoid glycals (**133c**, **76b**, **132c** and **136c**) with pyrimidine bases afforded 2′-deoxy-2′-iodo nucleosides (**678–684**) (Scheme 117).[84]

In 1999, Kim and coworker described stereoselective synthesis of 1′-β-2′,3′-dideoxy-2′-bis(ethoxycarbonyl)methyluridine nucleosides (**687a–e**) and (**688a–e**) in good yields from furanoid glycals **404** and **610**. Cyclopropanation of furanoid glycals **404**, **610** with diethyl diazomalonate and dirhodium tetraacetate (N$_2$C(CO$_2$Et)$_2$: Rh$_2$(OAc)$_4$: glycal = 2 : 0.01 : 1) afforded stereoselectively cyclopropanated sugars **685** and **686** respectively. Lewis acid mediated glycosylations of **685** and **686** with 5-substituted uracils afforded 1′β-2′,3′-dideoxy-2′-



Scheme 115

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Table 16 Stereoselectivity in the synthesis of 2′-phenylselenenyl nucleosides derived from *erythro* glycals[a]

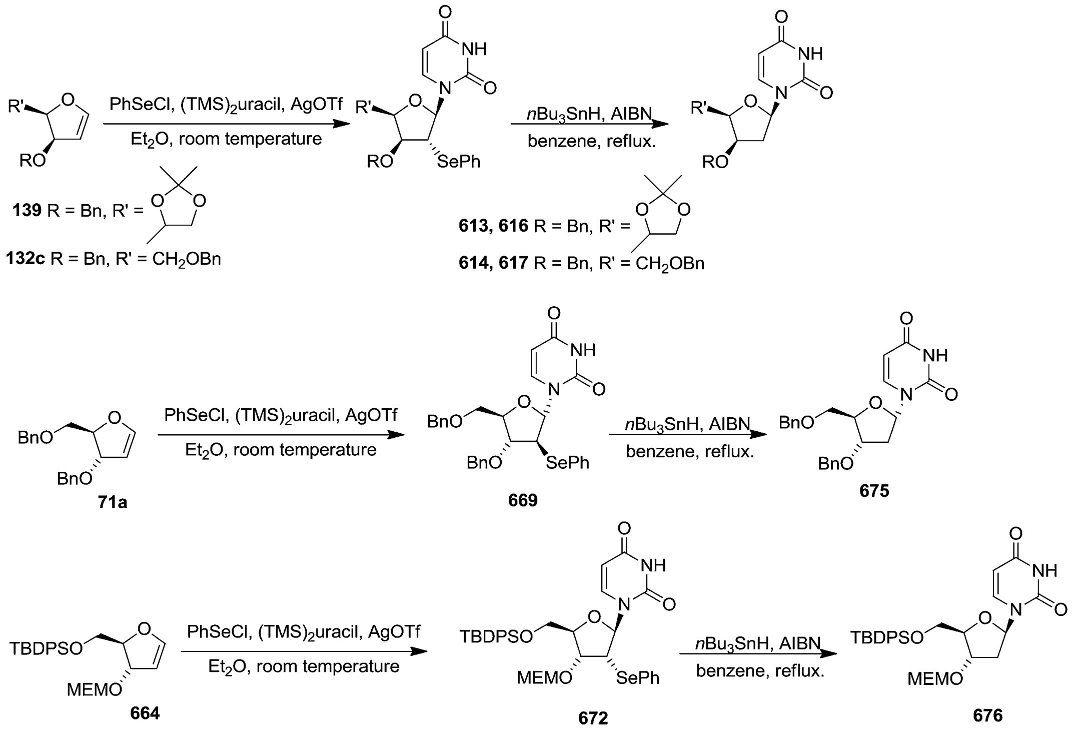
Starting glycals	Time (h)	Yield (%)	2′-Selenenyl nucleosides	(Diastereomeric ratio) (β-ribo : α-ribo : α-arabino : β-arabino) **B : C : D : E**			
661 R_1 = MEM, R_2 = Bn	2	82	**666** R_1 = MEM, R_2 = Bn	14	—	49	—
			666a R_1 = OH, R_2 = Bn	—	—	37	—
662 R_1 = TBDMS, R_2 = Bn	1.5	87	**667** R_1 = TBDMS, R_2 = Bn	32	16	16	—
			667a R_1 = OH, R_2 = Bn	18	5	13	—
66e R_1 = TBDMS, R_2 = TBDMS	1.5	88	**668** R_1 = TBDMS, R_2 = TBDMS	28	21	15	—
			668a R_1 = OH, R_2 = TBDMS	22	8	6	—
71a R_1 = Bn, R_2 = Bn	1	89	**669** R_1 = Bn, R_2 = Bn	30	—	70	—
90 R_1 = TBDPS, R_2 = Bn	2	58	**670** R_1 = TBDPS, R_2 = Bn	44	9	—	—
			670a R_1 = TBDPS, R_2 = Bn, R = SePh[b]	19	8	6	14
663 R_1 = Bn, R_2 = TBDPS	2	85	**671** R_1 = Bn, R_2 = TBDPS	43	11	32	14
664 R_1 = TBDPS, R_2 = MEM	2	83	**672** R_1 = TBDPS, R_2 = MEM	54	18	15	4
			672a R_1 = TBDPS, R_2 = MEM, R = SePh[b]	9	—	—	—
665 R_1 = Ac, R_2 = TBDPS	2	84	**673** R_1 = Ac, R_2 = TBDPS	23	14	16	6
			673a R_1 = Ac, R_2 = TBDPS, R = SePh[b]	26	5	5	5
66j R_1 = TBDPS, R_2 = TBDMS	2	87	**674** R_1 = TBDPS, R_2 = TBDMS	66	20	14	—

[a] Reactions were carried out at room temperature using the molar ratio glycal/PhSeCl/AgOTf/Uracil$(TMS)_2$ = 1/1.5/1.7/2. [b] R = SePh stands for selenenylation of nucleosides at position 5.

bis(ethoxycarbonyl)methyluridine nucleosides (**687a–e**) and (**688a–e**) respectively in good yields (Scheme 118).[85]

In 1999, Paquette and group showed furanoid glycals which are amenable to C-5 metalation in the presence of *t*BuLi, were readily coupled to N-protected 2,3-azetidinediones.[86] L-Glutamic acid derived[79] (*S*)-(+)-dihydro-5-(hydroxymethyl)-2-(3,4)-furanone **599** was converted to **689** and **690** by TrCl and TBDMSCl respectively. Their DIBALH reduction followed by acetylation of the resulting lactols yielded **691** and **692** respectively whose vacuum pyrolysis in a Kugelrohr apparatus afforded **693** and **270** respectively (Scheme 119). Also, exposure of the lithium derivative of **693** to excess nBu_3SnCl afforded **694** in 60% yield. They also treated **270** with KO^{t}Bu in the presence of PhSCl and PhSeCl to afford **695** and **696** respectively.

These furanoid glycals (**693, 270, 404, 695, 696** and **610**) in the presence of *t*BuLi were readily coupled to N-protected 2,3-azetidinediones (**697** and **698**) at low temperature in THF containing $BF_3 \cdot Et_2O$ to give the desired epimeric mixture of carbinols, *i.e.*



Scheme 116

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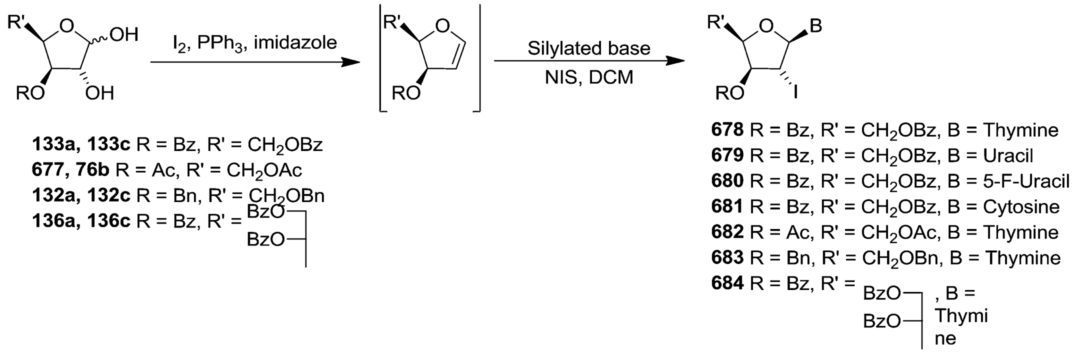
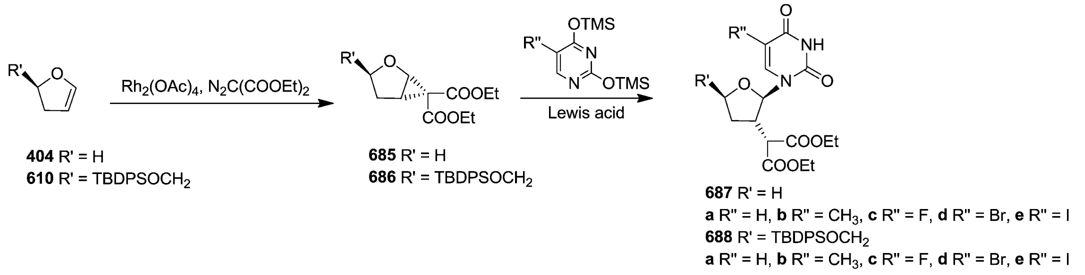
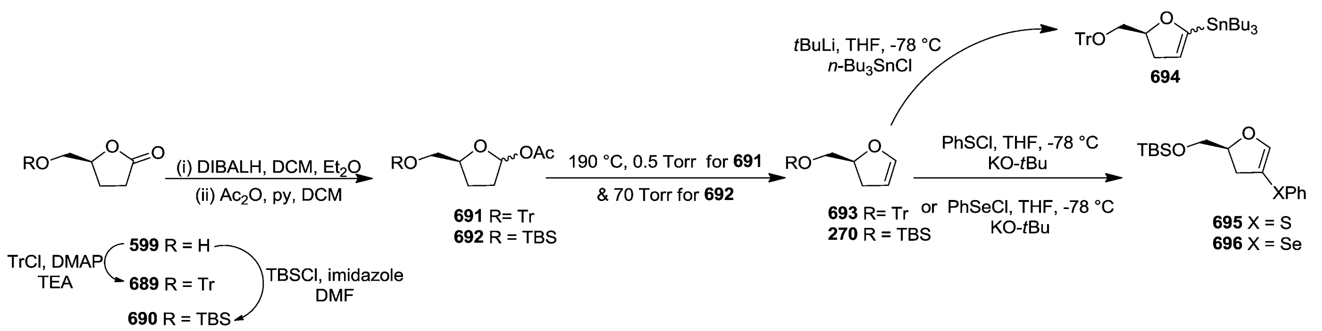


Scheme 117



Scheme 118



Scheme 119

(699–704) respectively. Treatment of (699–703) with pyridinium *p*-toluenesulfonate (PPTS) in benzene afforded spirocyclic keto amides (**705**, **706**, **707**, **708**, **709**, **710**, **711**) respectively (Scheme 120).

In 2001 Quirion and group reported the synthesis of 2′-deoxy-2′-difluoromethyluridine **716**.[87]

They described two methods A and B for its synthesis. One of them was started from thymidine **64a** which was converted into benzylated furanoid glycal **71a** (56% overall yield) in two steps involving the treatment of **64a** with an excess of HMDS in the presence of $(NH_4)_2SO_4$ followed by benzylation with BnBr of the resulting **65a**. Then they applied Miethchen method[88] on **71a** to obtain **712** which was acetylated to **713** (47% yield from **71a**). It was then converted to **714** *via* a radical reductive process (nBu$_3$SnH, AIBN). Addition of $(TMS)_2$uracil to **714** in the presence of TMSOTf furnished a 4 : 1 mixture of isomeric nucleosides in 76% yield. The major one was **715α** (NMR) whose hydrogenolysis afforded 2′-deoxy-2′-difluoromethyluridine **716α** (Scheme 121, method A).

In order to change the α/β ratio in favour of β, they synthesized α-halodeoxyarabinose **717** from **714** on treatment with HCl. The condensation of **717** in DCM with $(TMS)_2$uracil gave a 57 : 43 mixture of **715β** and **715α** isomers (NMR), respectively, *via* a S_N2 type reaction. Finally, the deprotection of the benzyl groups was easily achieved by hydrogenolysis of **715β** and **715α** to give the two desired nucleosides **716β** and **716α** with good yields (Scheme 122, method B).

In 2005, Choudhury and Pierce *et al.* synthesized D-D4FC **724** from an aromatization prone xylo-furanoid glycal **721**, by development of a palladium mediated Ferrier rearrangement-type glycosidation.[89] For the synthesis of xylo-furanoid glycal **721**, they chose commercially available 1,2-isopropylidine D-(+)-xylofuranose **718**, as the starting material. The free hydroxyl groups of **718** were then protected with *p*-anisoyl chloride in pyridine to afford **719**. The acetonide deprotection followed by treatment of the diols **720** with I_2/resin bound Ph_3P/imidazole afforded xylo-furanoid glycal **721** in more than 90% yield. After several trial and error for the choice of solvent, base and

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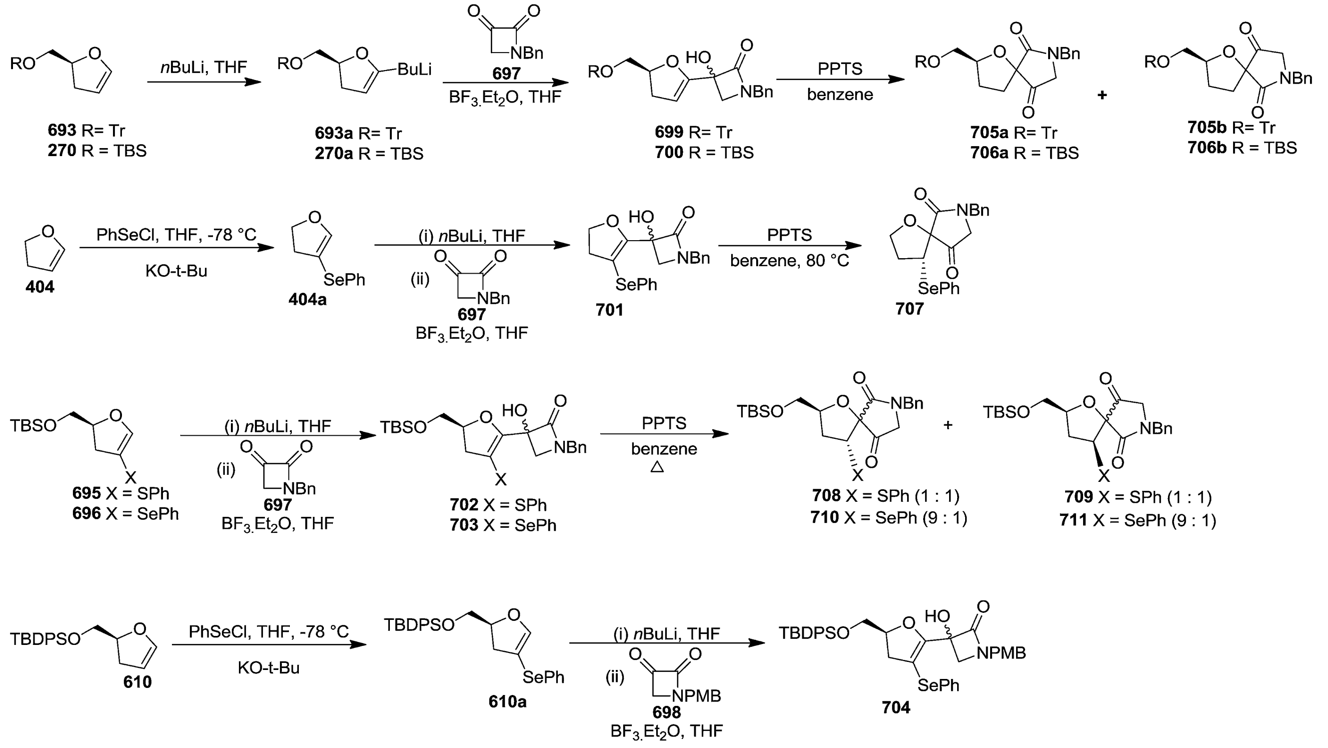
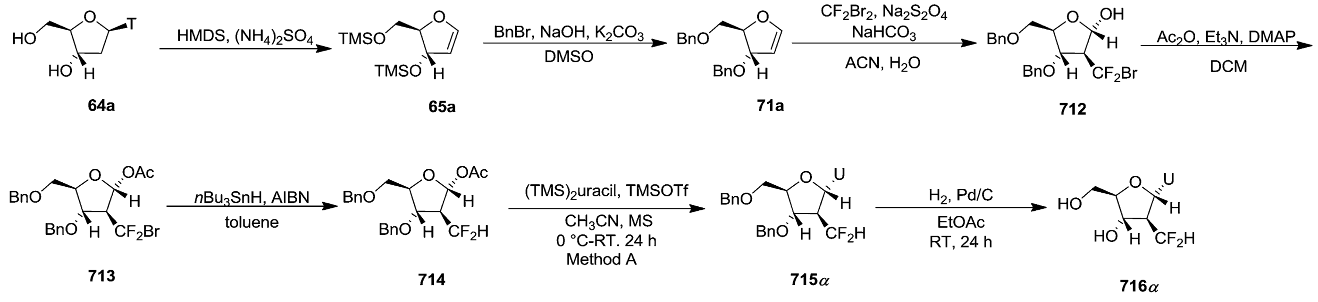


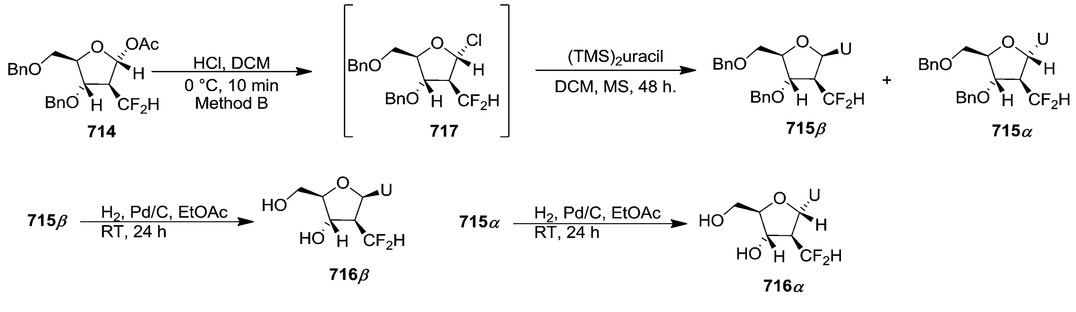
Scheme 120

different mol% of $Pd(Ph_3P)_4$, the glycosylation reaction of glycal **721** with an unprotected nucleoside base fluoro cytosine **722** was optimized with DBU as the base, NMP as the solvent with 3 mol% of $Pd(Ph_3P)_4$ as the catalyst at 33 °C for 2 days to afford 5′-anisoyl-D-D4FC **723** in good isolated yield. Deprotection of **723** provided the D-D4FC **724** in 82% yield (Scheme 123).

In 2006, Lequeux and group reported an alternative strategy based on group transfer reaction of *S*-alkyl dithiocarbonates (xanthates) followed by substitution reactions to prepare 2,3-*trans* disubstituted tetrahydrofuran derivatives.[90] They described the additions of alkyl radicals to 2,3-dihydrofuran derivatives using *S*-alkyl dithiocarbonates and the nucleophilic



Scheme 121



Scheme 122

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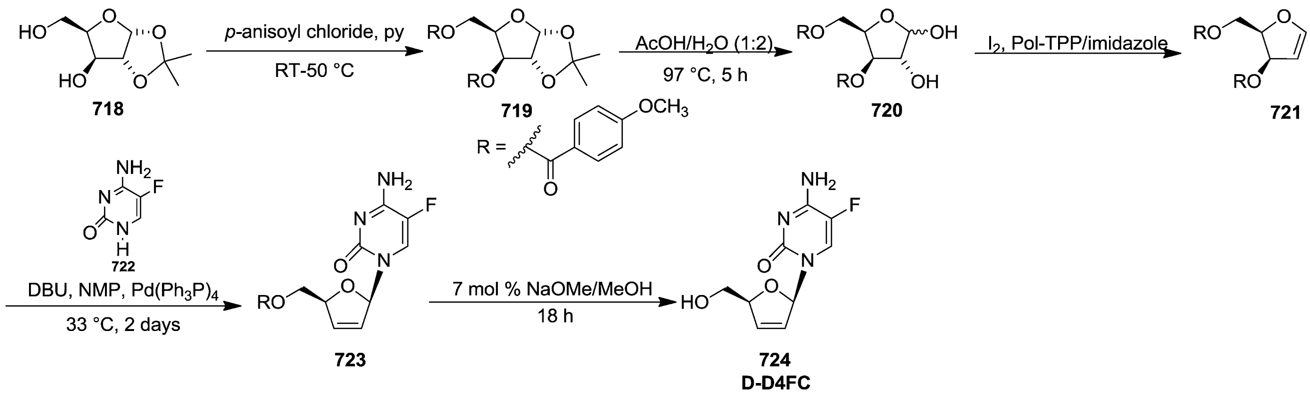
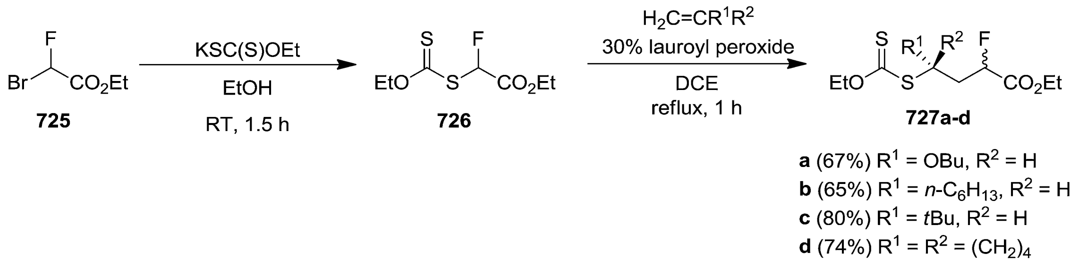
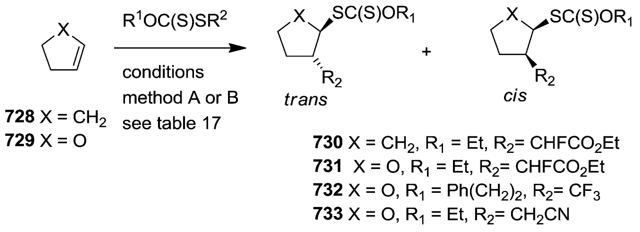


Scheme 123



Scheme 124



Scheme 125

displacements of the resulting anomeric *S*-alkyl dithiocarbonate function by various nucleophiles in the presence of Lewis acid to form a new carbon–carbon or carbon–heteroatom bond which presented a new route for the preparation of modified 2′-β-*C*-branched nucleoside analogues.

To achieve the goal, first they synthesized xanthate **726** following known procedure from commercially available ethyl bromofluoroacetate **725** (Scheme 124) by a nucleophilic substitution of its bromine atom with *O*-ethyl potassium dithiocarbonate.[91]

Then they studied the ethyl fluoroacetate group transfer reaction with the slow addition of lauroyl peroxide (30%) over 1 h in the mixture of different terminal alkenes (1.1 equiv.) and xanthate **726** in refluxing DCM (Scheme 124) to form fluoroesters (**727a–d**) in fair to good yields as a mixture of diastereomers (1 : 1 ratio).

They further repeated the same reaction (described for Scheme 124) with cyclopentene **728** and 2,3-dihydrofuran **729** in the presence of lauroyl peroxide. The best results were obtained from these alkenes (**728**, **729**) and the fluoroxanthate **726** (Scheme 125, Table 17, entries 1 and 2, method A) when lauroyl

Table 17 Group transfer reaction from cyclic alkenes[a]

Entry	Alkene	Xanthate $R^1OC(S)SR^2$	Method	Yield (%)	*Trans*/*cis* dr	Product
1	$X = CH_2$	**726**: R^1 = Et, R^2 = $CHFCO_2Et$	**A**	79	>98 : 2	**730**
			B	67		
2	X = O	**726**	**A**	81	>98 : 2	**731**
			B	73		
3	X = O	**734**: R^1 = $Ph(CH_2)_2$, R_2 = CF_3	**A**	30	>98 : 2	**732**
			B[b]	52		
4	X = O	**735**: R^1 = Et, R^2 = CH_2CN	**B**	55	9 : 1	**733**

[a] Method (A): slow addition of 0.3 equiv. of lauroyl peroxide, refluxed DCE, 1–2 h. Method (B): addition of 3 × 0.1 equiv. of Et_3B, DCM, room temperature, 1–2 h. [b] Stirring was maintained overnight at room temperature.

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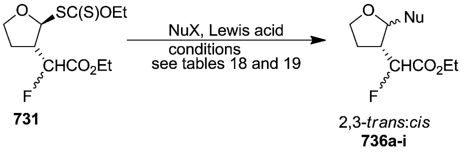


Scheme 126

peroxide was added slowly to a mixture of alkene and xanthate (method A). In case of cyclopentene (X = CH$_2$) **728**, only two diastereomers were detected in a 1 : 1 ratio, and purification of the crude product afforded 2,3-*trans* disubstituted cyclopentane derivatives **730** in 79% yield. Similar results were observed from the 2,3-dihydrofuran (X = O) **729** and xanthate **726**, and a mixture of two *trans* diastereomers of **731** (2,3-*trans* disubstituted tetrahydrofuran derivatives, ^{1}H{^{19}F} HOESY) was obtained in 81% yield. These two isomers of **731** differed only by the relative configuration of the third stereogenic center bearing the fluorine atom. The *cis* products were not reported in both cases (cyclopentene and 2,3-dihydrofuran). 2,3-*trans* Isomers **732** were obtained from **729** in the case of xanthate **734** in 30% isolated yield (Scheme 125, Table 17, entry 3, method A).

They also repeated the reaction with Et$_3$B, as an alternative free radical initiator of lauroyl peroxide, in deoxygenated DCM under N$_2$ atmosphere (method B) to afford 2,3-*trans* products **730** in 67% isolated yield from **728** and xanthate **726** (Table 17, entry 1, method B). While 2,3-*trans* disubstituted furans **731** were isolated in 73% yield from 2,3-dihydrofuran **729** and xanthate **726** (Table 17, entry 2, method B), the reaction between **729** and the trifluoromethylxanthate **734** afforded the *trans* adduct **732** in 52% yield (Table 17, entry 3, method B). The reaction proceeded smoothly with xanthate **735** and afforded the 2,3-*trans* isomers **733** as major products in 55% yield (Table 17, entry 4, method B).

Afterward, they explored the formation of a new carbon–carbon or carbon–heteroatom bond by displacement of dithiocarbonate function of **731** by a variety of nucleophiles in the presence of Lewis acid (Scheme 126, Tables 18 and 19).

By following this strategy, they have synthesized 2′-deoxy-2′-*C*-β-alkyl nucleoside analogues **739** from furanoid glycal **71a** and xanthate **726** (Scheme 127). Lauroyl peroxide was added slowly in the reaction mixture of furanoid glycal **71a** and xanthate **726** in DCE and the reaction mixture was refluxed for 5 h to obtain a diastereomeric mixture of 2,3-*trans* addition products **737** (1 : 1) in 57% isolated yield. Treatment of (TMS)$_2$thymine with **737** in the presence of AgOTf at 0 °C for 3 h afforded a mixture of protected 2′-deoxy-2′-*C*-β-alkyl nucleoside analogues **738** in 61% yield (only *trans* products). These were subjected to hydrogenation to give the corresponding diol **739**.

The synthesis of furanoid glycals (**171**, **173**) proposed by Haraguchi and group has been already discussed in Scheme 30.[38] Now, the utilization of their synthesized furanoid glycals (**66e**, **171** and **173**) is being discussed here for the synthesis of 2′-deoxynucleosides and its 1′-branched analogues. They performed NIS-mediated electrophilic glycosidation between protected *erythro*-furanoid glycals (**66e**, **171** and **173**) and silylated thymine in CH$_3$CN/DCM at room temperature and observed that only the glycal **173** selectively furnished β-anomer **742** exclusively in 76% yield. Whereas, under identical reaction condition formation of the α-anomer (**740α**, 62% yield)

Table 18 Carbon–oxygen and carbon–carbon bond formation

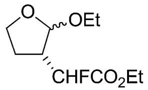
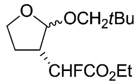
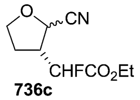
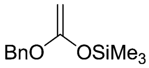
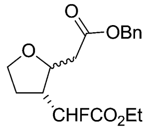
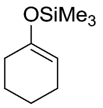
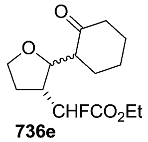
Entry	Nu-X	Conditions	Lewis acids	Products	Yields (%)	*Trans*/*cis* dr
1	EtOH	Toluene, 20 °C, 15 min	AgOTf	 **736a**	72	7 : 3
2	*t*BuCH$_2$OH	Toluene, −17 °C, 1 h	AgOTf	 **736b**	73	3 : 2
3	Me$_3$SiCN	Toluene, −78 °C, 2.5 h	SnCl$_4$	 **736c**	83	9 : 1
4		Toluene, −17 °C, 2 h	AgOTf	 **736d**	36	4 : 1
5		Toluene, −17 °C, 1 h	AgOTf	 **736e**	32	>98 : 2

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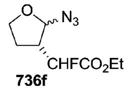
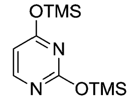
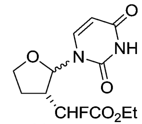
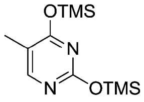
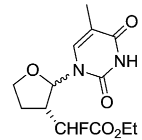
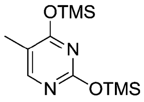
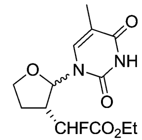
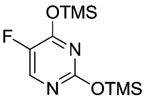
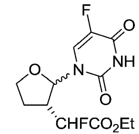
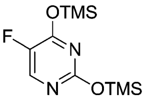
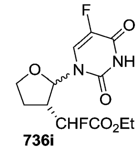
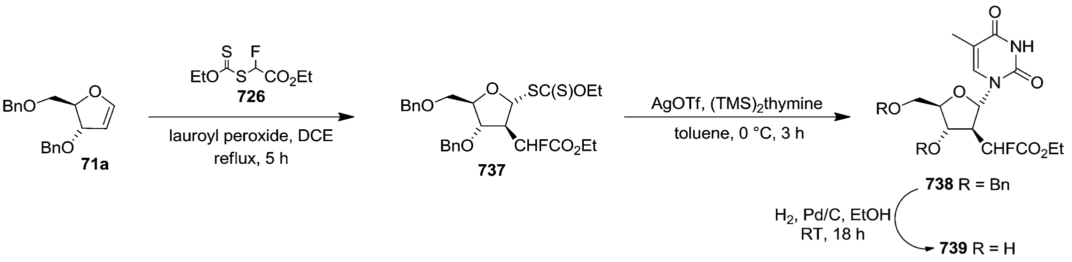
Table 19 Carbon–nitrogen bond formation

Entry	Nu-X	Conditions	Lewis acids	Products	Yields (%)	*Trans*/*cis* dr
1	Me_3SiN_3	Toluene, −17 °C, 1 h	AgOTf	 **736f**	68	3 : 2
2		Toluene, −17 °C, 2 h	AgOTf	 **736g**	63	9 : 1
3		Toluene, −17 °C, 1.5 h	AgOTf	 **736h**	83	9 : 1
4		Toluene, −17 °C, 4 h	Cu(OTf)$_2$	 **736h**	76	9 : 1
5		Toluene, −17 °C, 1.5 h	AgOTf	 **736i**	45	4 : 1
6		Toluene, −17 °C, 3.5 h	Cu(OTf)$_2$	 **736i**	25	4 : 1



Scheme 127

dominated over that of the β-anomer (**740β**, 15% yield) in the case of glycal **66e**. On the other hand, glycal **171** gave equal amounts of the β-(**741β**, 35% yield) and α-(**741α**, 35% yield) anomers (Scheme 128, Table 20).

They further showed the electrophilic glycosidation of silylated uracil, N^4-(acetyl)cytosine with glycal **173** also gave β-anomer respectively in exclusive amount: **743** (76% yield); **744** (55% yield) (Fig. 6). But in the case of silylated N^6-(benzoyl) adenine desired N^9-glycoside **745** was formed only 26% yield along with N^7-(**746**, 17% yield) and N^1-(**747**, 13% yield) isomers.

The glycosidation products (**742–745**) were converted to the corresponding 2′-deoxynucleosides (**748–751**) in good yields by reacting each with nBu$_3$SnH, Et$_3$B/O$_2$ in toluene at room temperature (Scheme 129).

They further showed the scope of this glycosidation method by the formation of several 1-alkyl and 1-(ω-hydroxy)alkyl *erythro*-furanoid glycals which also gave the respective β-anomer exclusively. Furanoid glycal **173** was lithiated with tBuLi (3 equiv.) in THF, which on treatment with several carbon electrophiles (Scheme 130, Table 21), afforded 1-alkyl *erythro*-furanoid glycals (**752**, **753**) and 1-(ω-hydroxy)alkyl *erythro*-

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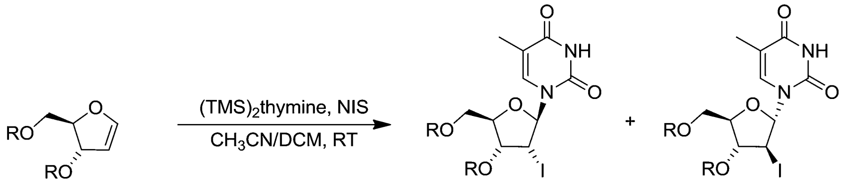


66e R = TBDMS

171 R = TIPDS

173 R = DTBS

740β R = TBDMS

741β R = TIPDS

742 R = DTBS

740α R = TBDMS

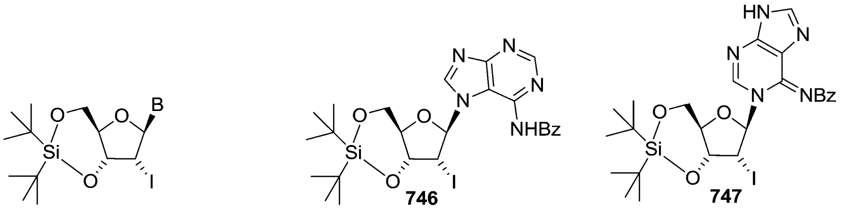
741α R = TIPDS

Scheme 128

Table 20 NIS-initiated electrophilic glycosidation of silylated thymine by using (**66e**, **171** and **173**)[a]

Entry	Glycal	Products (isolated yield)	Ratio of β-anomer/α-anomer
1	**66e**	**740β** and **740α** (77%)	1 : 4
2	**171**	**741β** (35%) and **741α** (35%)	1 : 1
3	**173**	**742** (76%)	—

[a] All reactions were carried out in CH_3CN/DCM at rt for 12 h by using $(TMS)_2$thymine (3.0 equiv.) and NIS (1.5 equiv.).



746

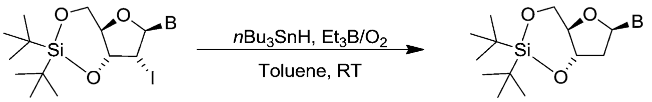
747

743 B = Uracil-1-yl

744 B = N^4-(acetyl)cytosine-1-yl

745 B = N^6-(benzoyl)adenine-9-yl

Fig. 6 Compounds (**743–747**).



742 B = Thymine-1-yl

743 B = Uracil-1-yl

744 B = N^4-(acetyl)cytosine-1-yl

745 B = N^6-(benzoyl)adenine-9-yl

748 B = Thymine-1-yl (84%)

749 B = Uracil-1-yl (100%)

750 B = N^4-(acetyl)cytosine-1-yl (79%)

751 B = N^6-(benzoyl)adenine-9-yl (94%)

Scheme 129

furanoid glycals (**754–759**). To obtain derivatives suitable for glycosidation, 1-(ω-hydroxy)alkyl *erythro*-furanoid glycals (**754–759**) were converted to their *O*-triethylsilyl derivatives (**760–765**) respectively on silylation (Scheme 130).

NIS-initiated electrophilic glycosidation of silylated thymine with these glycals (**752**, **753**, and **760–765**) formed exclusively the β-anomers of 1′-branched 2′-iodothymidine derivatives (**766–773**) respectively. Compounds (**766–773**) were transformed to 1′-branched thymidines (**774–781**) in good yields (Scheme 131, yields are given in parentheses) by reacting them with $n\mathrm{Bu_3SnH}$, Et_3B/O_2, in toluene at room temperature.

Pal and Shaw have already reported the synthesis of four stereochemically different enantiomerically pure, furanoid glycal building blocks (**162a–c, 139**) (Scheme 28) (Fig. 3)[35] and also shown their synthetic utility to obtain some natural products

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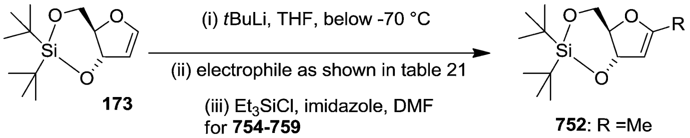


173

752: R =Me
753: R =CH_2Ph
754: R =CH_2OH
755: R =CH(OH)Ph
756 R =CH(OH)Me
757: R =$CH(OH)Me_2$
758: R =CH_2CH_2OH
759: R =$CH_2CH_2CH_2OH$

760: R =CH_2OSiEt_3 (86%)
761: R =$CH(OSiEt_3)Ph$(85%)
762: R =$CH(OSiEt_3)Me$(93%)
763: R =$C(OSiEt_3)Me_2$ (95%)
764 R =$CH_2CH_2OSiEt_3$ (85%)
765: R =$CH_2CH_2CH_2OSiEt_3$ (63%)

Scheme 130

Table 21 Preparation of 1-alkyl and 1-(ω-hydroxy)alkyl glycals based on lithiation of **173**[a]

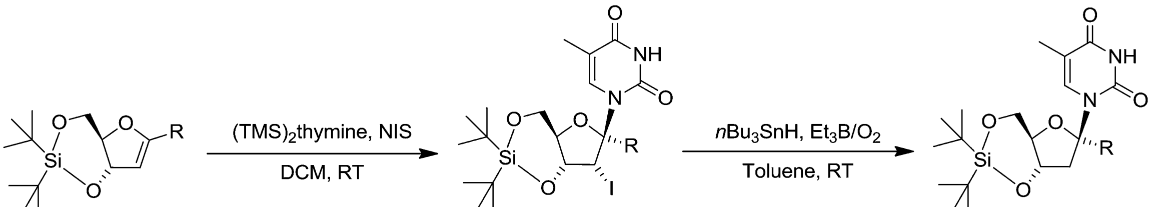
Entry	Electrophile (equiv.)	R	Product (isolated yield)
1	MeI (10)/HMPA (5)	Me	**752** (56%)
2	$PhCH_2Br$ (5)/HMPA (10)[b]	CH_2Ph	**753** (56%)
3	DMF (5) then $NaBH_4$ (1.5)	CH_2OH	**754** (82%)
4	PhCHO (3)	CH(OH)Ph	**755** (93%)[c]
5	MeCHO (5)	CH(OH)Me	**756** (90%)[c]
6	CH_3COCH_3 (5)	$C(OH)Me_2$	**757** (19%)[d]
7	Ethylene oxide (5) & $BF_3 \cdot OEt_2$ (5)	CH_2CH_2OH	**758** (62%)
8	Trimethylene oxide (5) & $BF_3 \cdot OEt_2$ (3)	$CH_2CH_2CH_2OH$	**759** (65%)

[a] After addition of the respective electrophile, the reaction mixture was stirred below −70 °C for 0.5 h, except entry 2. [b] After addition of the electrophile,the reaction mixture was stirred at −40 °C for 11 h. [c] The product was obtained as a mixture of diastereomers. [d] The starting material (**173**) was recovered in 78% yield.

such as the aggregation pheromones brevicomins (**285a–d**) (Schemes 47–50) and styryllactones (+)-cardiobutanolide (**290a**, Scheme 51), (−)-cardiobutanolide (**290b**, Scheme 52) and (+)-goniofufurone (**295a**, Scheme 53).[2h] Thus, inspired by literature reports on the interesting and important biological activities of 2′-deoxynucleosides we decided to undertake the synthesis of six 2′-deoxynucleoside analogue building blocks (Fig. 7) from the stereochemically different furanoid glycals (**162a–c**, **139**) by adopting a methodology reported earlier by Kim and Misco.[9] We have synthesized three pairs of enantiomeric 2′-deoxynucleoside analogues (**783a**, **783b**), (**783c**, **783e**) and (**783d**, **783f**) respectively as building blocks from furanoid glycals (**162a–c, 139**) by involving the similar synthetic strategy.[2i]

Furanoid glycal **139** on treatment with $(TMS)_2$thymine (2.0 equiv.) in the presence of NIS (2.5 equiv.) in dry DCM at −30 °C → rt for overnight afforded glycosylated product **782a**, which, without purification, was directly converted into 2′-deoxynucleoside analogue **783a** in 26% yield (over two steps) in the presence of *n*Bu_3SnH and a radical initiator ABCN (1,1′-Azobis-(cyclohexanecarbonitrile)) (Scheme 132). The stereochemistry of compound **783a** was determined on the basis of its NOE spectrum.

Having this result in hand, we further extended our study on furanoid glycal **162a** which was an optical antipode of **139**. Thus 2′-deoxynucleoside analogue **783b** (Scheme 133) was obtained from **162a** following the identical reaction pathway



752, 753 and **760-765**

766: R =Me(57%)
767: R =CH_2Ph (55%)
768: R =CH_2OSiEt_3 (71%)
769a: R=$CH(OSiEt_3)Ph$
(45%,less polar product)
769b: R =$CH(OSiEt_3)Ph$
(45%,more polar product)
770a: R=$CH(OSiEt_3)Me$
(45%,less polar product)
770b: R =$CH(OSiEt_3)Me$
(45%,more polar product)
771: R =$C(OSiEt_3)Me_2$ (34%)
772: R =$CH_2CH_2OSiEt_3$ (58%)
773 R =$CH_2CH_2CH_2OSiEt_3$ (48%)

774 R =Me(100%)
775: R =CH_2Ph (93%)
776: R =CH_2OSiEt_3 (100%)
777a: R =$CH(OSiEt_3)Ph$(94%)
777b: R =$CH(OSiEt_3)Ph$ (99%)
778a: R =$CH(OSiEt_3)Me$(92%)
778b: R =$CH(OSiEt_3)Me$(94%)
779: R =$C(OSiEt_3)Me_2$ (92%)
780: R =$CH_2CH_2OSiEt_3$ (100%)
781: R =$CH_2CH_2CH_2OSiEt_3$ (78%)

Scheme 131

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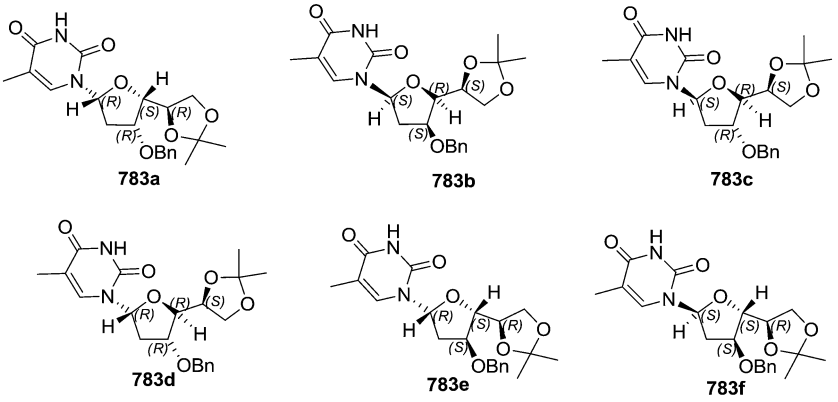
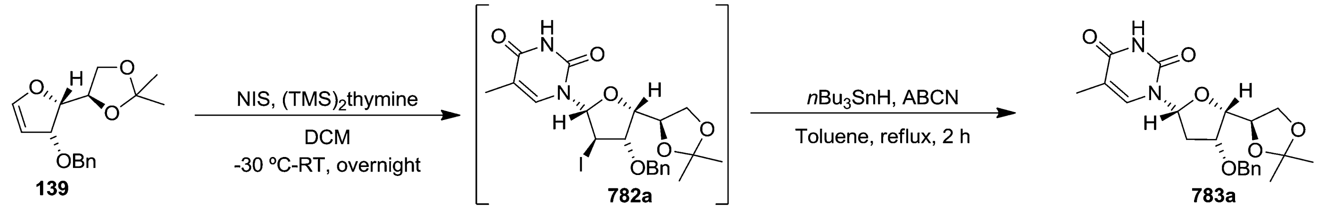
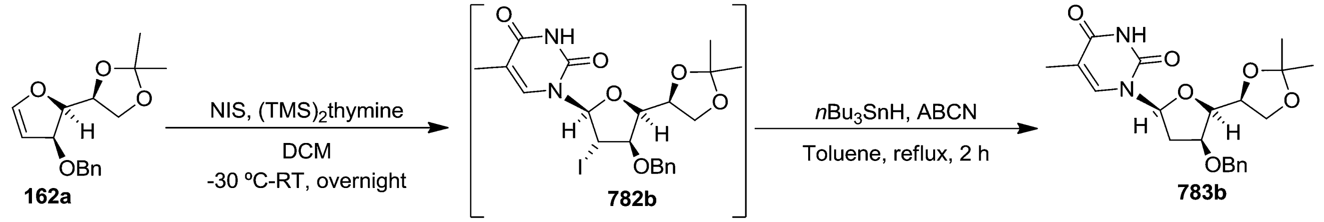


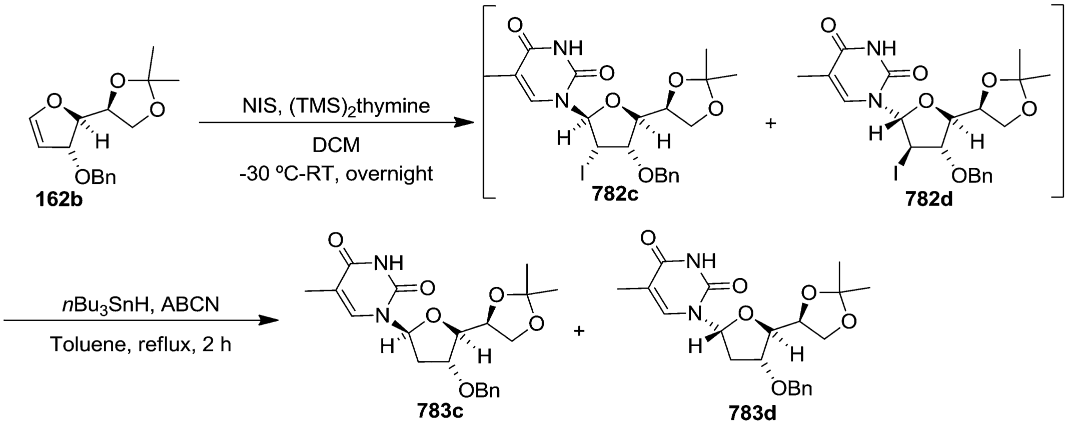
Fig. 7 Structures of 2′-deoxynucleoside analogues (**783a–f**).



Scheme 132



Scheme 133



Scheme 134

as it was shown in the case of **783a** (Scheme 132). The $[\alpha]_D$ of 2′-deoxynucleoside analogue **783b** $[[\alpha]_D^{25} + 17.7$ (c 0.27, MeOH)] was just opposite to that of **783a** $[[\alpha]_D^{25} - 23.4$ (c 1.67, MeOH)].

Our further study on *erythro*-furanoid glycal **162b**, under the identical reaction conditions furnished a mixture of two compounds. Column chromatographic purification of the mixture led to the isolation of **783c** and **783d** in 8% and 32%

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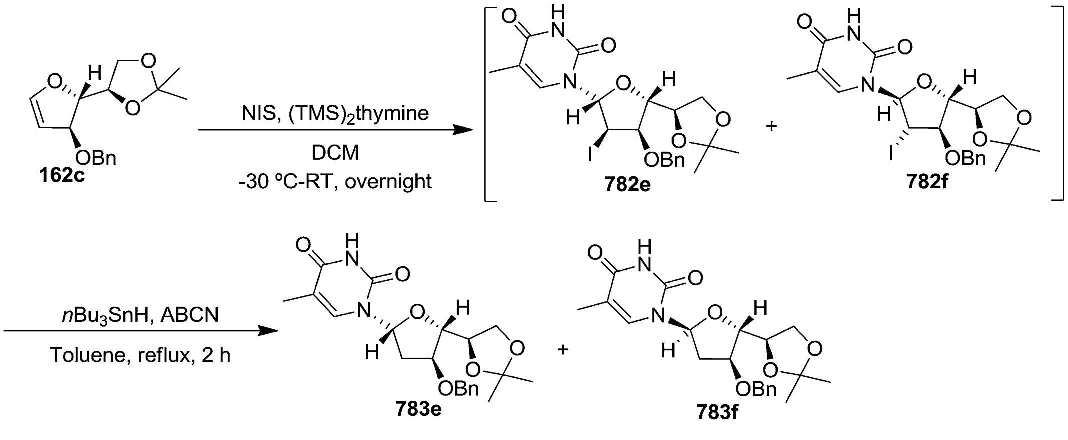

Scheme 135

yields respectively (over two steps, Scheme 134). The NOE experiment was also carried out for the complete characterization of 2′-deoxy-β-nucleoside analogue **783c** [$[\alpha]_D^{25} - 1.91$ (*c* 0.10, MeOH)] and 2′-deoxy-α-nucleoside analogue **783d** [$[\alpha]_D^{26} - 10.2$ (*c* 0.40, MeOH)] in a 1 : 4 ratio.

Under the identical reaction conditions formation of mixture of nucleosides was quite obvious from *erythro*-furanoid glycal **162c** having two *anti* bulky groups at C-3′ and C-4′ which was enantiomeric to **162b**. The chromatographic purification of the mixture containing the isomeric nucleoside analogues led to the isolation of 2′-deoxynucleoside analogues **783f** [$[\alpha]_D^{26} + 12.1$ (*c* 0.57, MeOH)] as the major product in 27% yield (over two steps) and **783e** [$[\alpha]_D^{25} + 1.42$ (*c* 0.37, MeOH)] as minor product in 9% yield (over two steps) (Scheme 135) which were the enantiomers of **783d** and **783c** respectively.

7. Conclusion

In summary, this review is an attempt to describe the various synthetic approaches to obtain both *erythro* and *threo* furanoid glycals since their discovery. Emphasis has also been given to their synthetic applications towards the syntheses of natural products, natural product like molecules, important "building blocks" and C-and N-nucleosides. One of the purposes, of this review is to attract the attention of the synthetic community to develop new approaches for furanoid glycals syntheses and to exploit this inexpensive and widely available chiral building blocks for broader applications both in synthetic as well as medicinal chemistry. We hope that this review will be useful to those who have an interest in furanoid glycals.

Acknowledgements

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Notes and references

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