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Division of Medicinal & Process Chemistry, CSIR- Central Drug Research Institut, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow-226 031, India. E-mail: akshaw55@yahoo.com; Tel: +91-9415403775

† CDRI Communication Number is 9482.



Pinki Pal was born in the state of West Bengal, India. She obtained her B.Sc. in Chemistry (Hons.) from The University of Burdwan, India and M.Sc. in Organic Chemistry from University of Kalyani, India in 2002 and 2004 respectively. She received her Ph.D. degree in 2011 jointly from CSIR-Central Drug Research Institute, Lucknow, and Jadavpur University, Kolkata, India, under the supervision of Dr Arun K.

Shaw (CSIR-CDRI) and co-supervision of Prof. Gourhari Maiti (Jadavpur University). In her doctoral research, she worked on 'chiron' approach to total stereoselective synthesis of bioactive natural product and natural product like molecules starting from commercially available monosaccharides. After working as a Project Associate at the Indian Institute of Science, India, with Prof. N. Jayaraman and Post-doctoral Fellow at National Taiwan University, Taiwan, with Prof. Ya-Ching Shen, she joined as Associate Scientist at GVK Biosciences Pvt. Ltd., Hyderabad, India. Later she worked as a Consultant at Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bangalore in Dr Jayanta Haldar's Research Group. At present, she is Lecturer at Department of Chemistry, Mount Carmel College Autonomous, Bangalore, India.

‡ Present address: Department of Chemistry, Mount Carmel College Autonomous, 58, Palace Road, Bangalore-560052, India. E-mail: pinkipal@gmail.com; Tel: +91-7760512715



Arun K. Shaw was born in Raniganj, West Bengal. He received his B.Sc. (Hons.) degree in Chemistry from Scottish Church College, Calcutta University, in 1975, his M.Sc. degree in Chemistry from Calcutta University in 1977, and his Ph.D. in Natural Product Chemistry under the supervision of Professor S. N. Ganguly from Bose Institute, Calcutta University, in 1985.

After his doctoral work, he worked with Professors S. K. Talapatra and B. Talapatra in the Department of Pure Chemistry, Calcutta University, during 1985–1986. In 1987 he joined as a Scientist Gr. IV (1) in the Department of Food Chemistry, CSIR-Central Food Technological Research Institute, Mysore. He moved in the same capacity to the Division of Medicinal Chemistry, CSIR-Central Drug Research Institute, Lucknow, in 1991. His research interests centred around isolation, purification characterization of natural products of plant origin, syntheses of bioactive natural product or natural product like molecules using carbohydrates as chiral pool. He is also interested in development of new methodology/synthetic reagents and investigation of new reaction pathways in organic synthesis. He has published over 78 papers in peer reviewed international journals including a review article in *Chemical Review*. He held the visiting scientist positions at University of Rostock, Germany under CSIR-DAAD Exchange Programme of scientists in April–June, 2000 and at University of Glasgow, Glasgow, Scotland in March, 2013 under INSA, New Delhi International Collaboration/Exchange Programme during 2011–2012. He superannuated in 2015 from Division of Medicinal Chemistry, CSIR-Central Drug Research Institute, Lucknow from the position of Chief Scientist and Professor AcSIR.



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.

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'-dideoxy nucleosides⁹ and more recently 2'-deoxynucleosides.¹⁰

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-dihydrofuran (**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 Zach¹¹ 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.

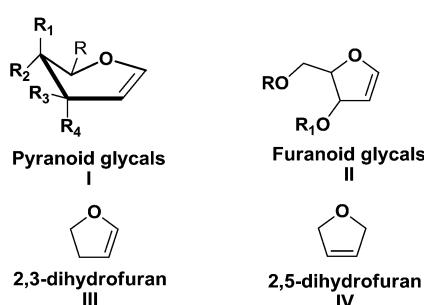
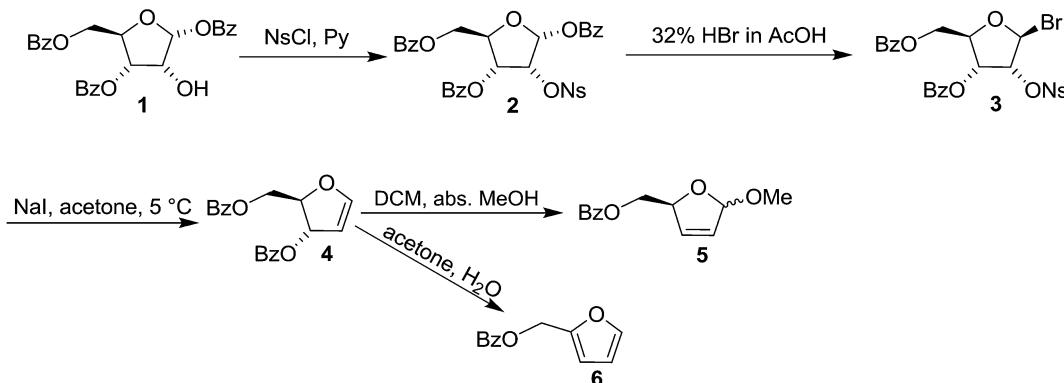


Fig. 1 General structures of pyranoid glycals (**I**), furanoid glycals (**II**), 2,3-dihydrofuran (**III**) and 2,5-dihydrofuran (**IV**).

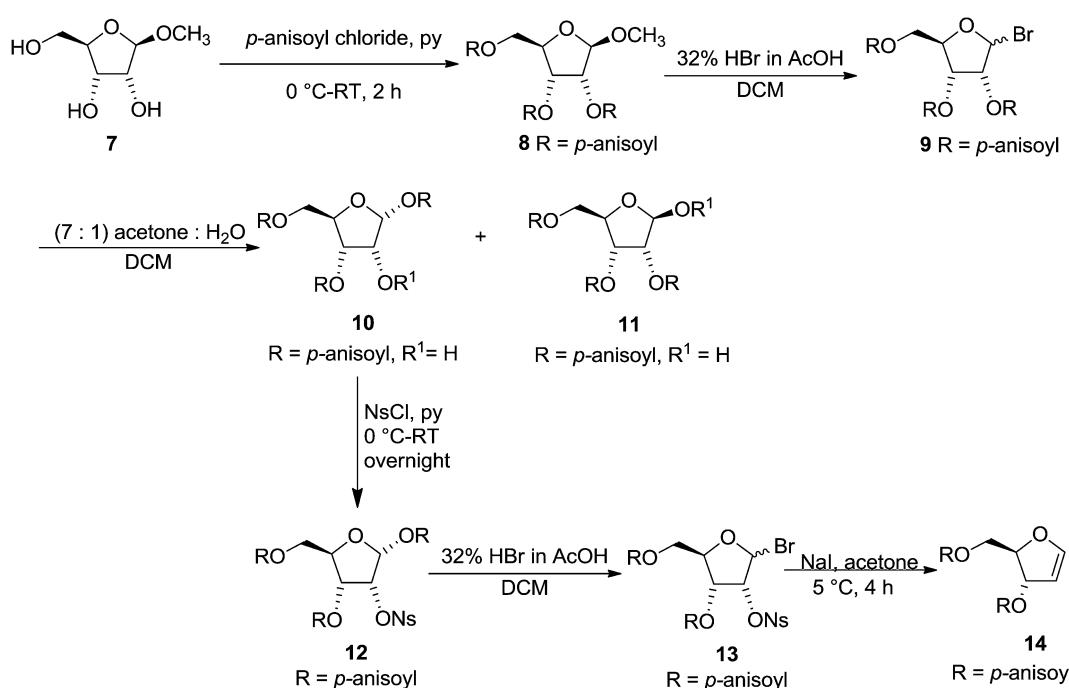




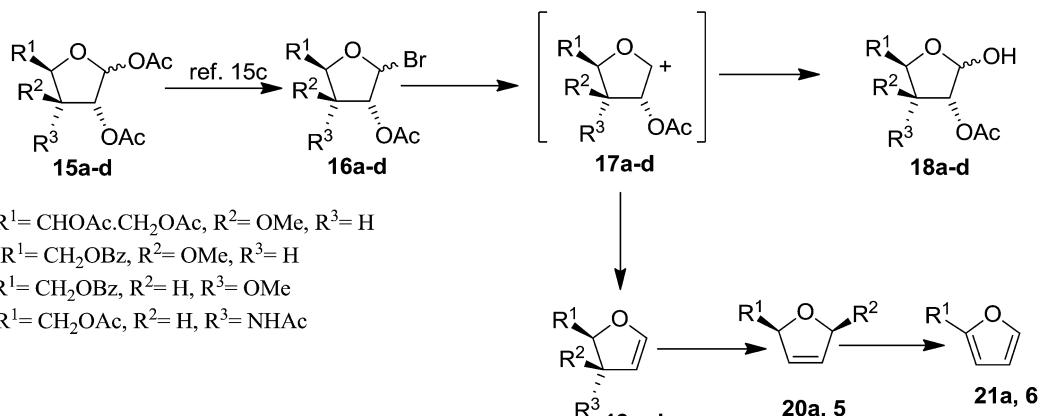
Scheme 1

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 FGs¹⁵ 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 acetyl anion to form the glycals (**19a-d**), or can combine with hydroxyl or acetyl 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 N₂ at -5 °C for 6 months. Compounds **20a** and **5** were



Scheme 2



Scheme 3

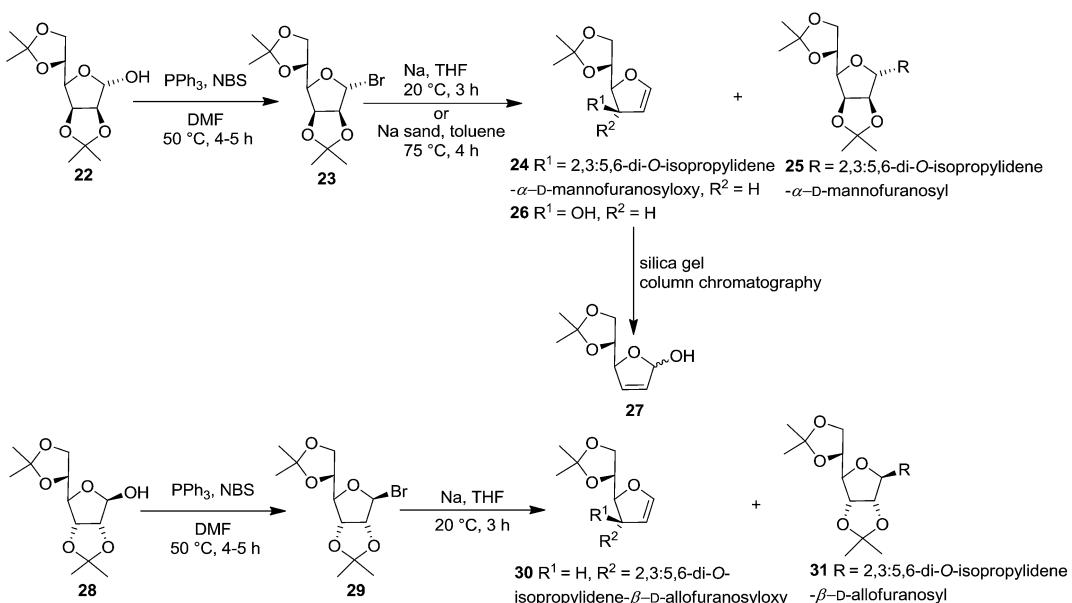
Table 1 Product yields of furanoid glycals (19a–d) by modified Fischer and Zach's method from substituted furanose derivatives (15a–d)

Starting material	Yields of products (%)				
	Furan (21a, 6)	Glycal (19a–d)	2,3-Unsaturated compound (20a, 5)	Starting 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. 16b) 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



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).

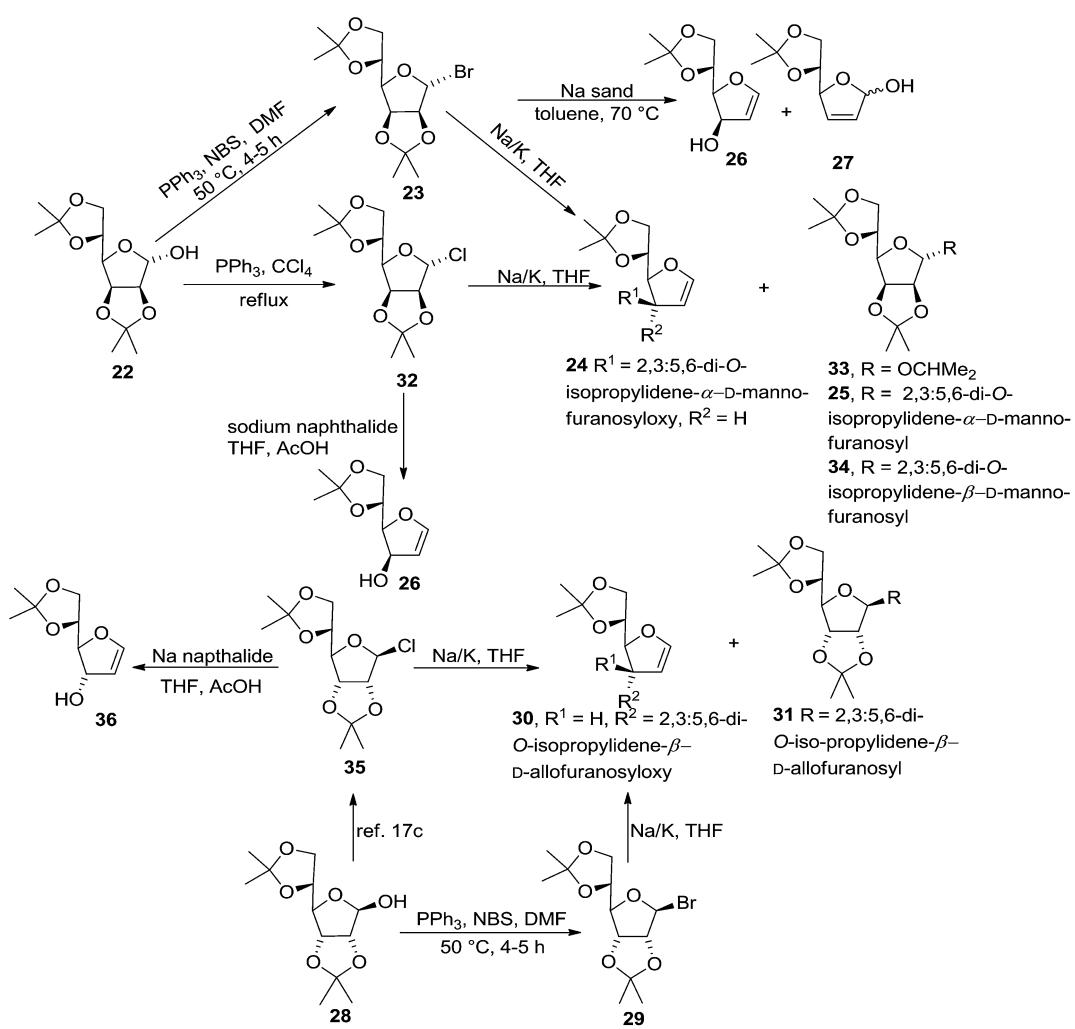
In 1978, the same group discussed an alternative route for the synthesis of furanoid and pyranoid glycals.^{17a} While treating 2,3:5,6-di-*O*-isopropylidene- α -D-mannofuranose **22** derived furanosyl chloride **32** (ref. 17b) with sodium naphthalide in THF followed by acetic acid furnished FG **26** 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. 17c) and the analogous bromide **29**, gave only the 3-*O*-furanosyl glycal **30** (69%) and a trace of the disaccharide **31** (Scheme 5).

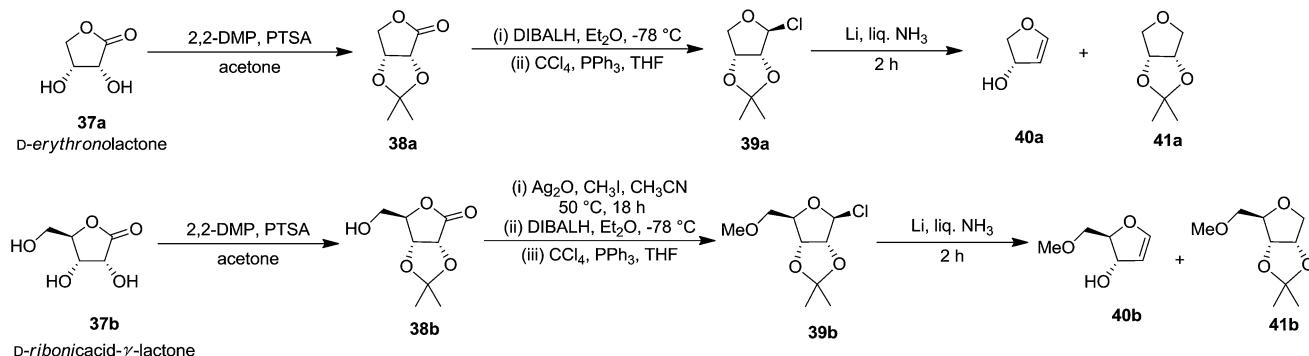
Further, warming furanosyl bromide **23** with sodium sand in toluene at 70 °C afforded the glycal **26** in low yield along with its isomeric 2,5-dihydro derivative **27** (Scheme 5).

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 Et₂O at -78 °C to an intermediate 2,3-*O*-isopropylidene-D-erythrose, which was immediately treated with CCl₄ and Ph₃P in THF to obtain furanosyl chloride **39a**. Its reduction with 4 equiv. of Li in liquid NH₃ in the presence of 6 equiv. of NH₄Cl 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

lactone was done by adopting the standard process to obtain acetonide **38b**. Methylation of its primary hydroxyl group with Ag₂O/CH₃I/CH₃CN at 50 °C for 18 h, followed by reduction of the resulting *O*-methyl derivative with DIBALH in Et₂O at -78 °C for 1 h gave hemiacetal in 90% overall yield, which on treatment with CCl₄/PPh₃/THF resulted furanosyl chloride **39b** in 90% yield. Its reduction with Li in liquid NH₃ 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).

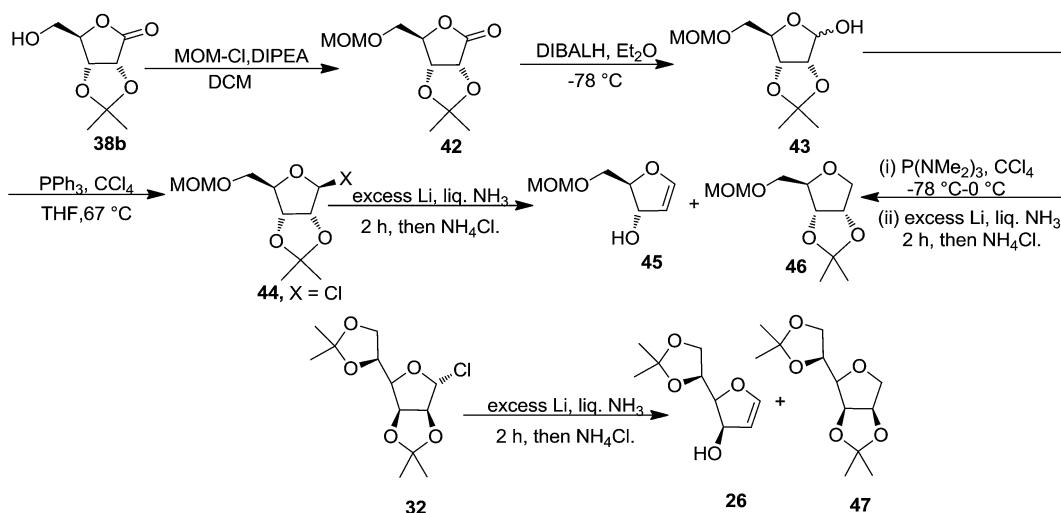
This group again utilized acetonide **38b** for the synthesis of furanoid glycal **45**.⁴ The MOM protected lactone **42**, prepared from **38b** by treating with chloromethyl methyl ether (MOMCl) in the presence of diisopropylethylamine ((ⁱPr)₂EtN) in DCM, on reduction with DIBAL-H at -78 °C provided lactol **43**. Its chlorination with PPh₃ and CCl₄ in THF gave the chloride **44**. Its reduction with Li in liquid NH₃ 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 CCl₄ in the presence of alcohols to form adducts of type **48** (Fig. 2).

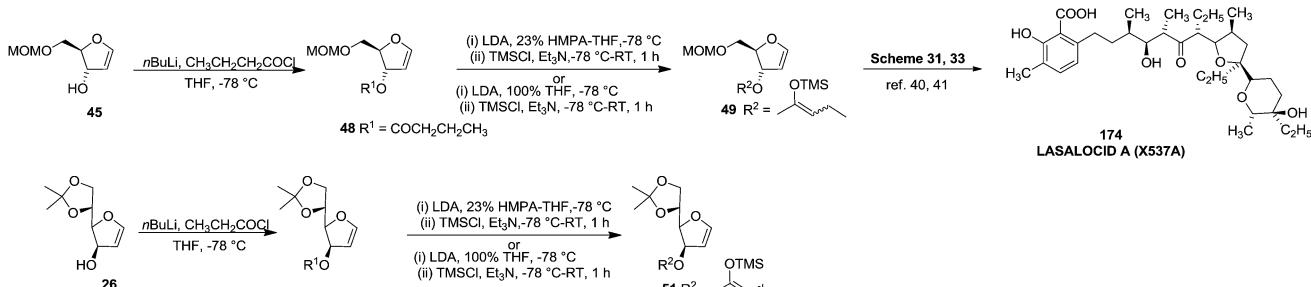
First TDAP was added to a solution of lactol **43** and CCl₄ in THF at -78 °C. The resulting reaction mixture was warmed to 0 °C and then immediately it was added to a solution of excess Li in liquid NH₃ to afford a mixture of **45** and **46** in 6 : 1 with 93% yield after passing the crude product 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

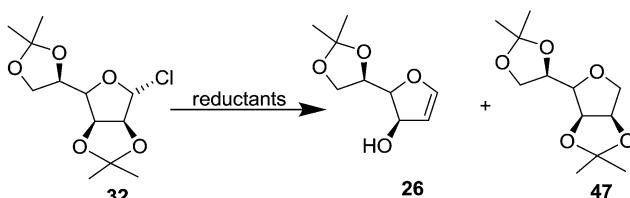
Fig. 2 Adduct **48**.

Scheme 7





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- <i>tert</i> -butylbiphenyl ^g	94%	>50 : 1

^a 35 equiv. of metal, 0.5 M, 1 : 10 THF/NH₃, -78 °C, 30 min, then NH₄Cl.

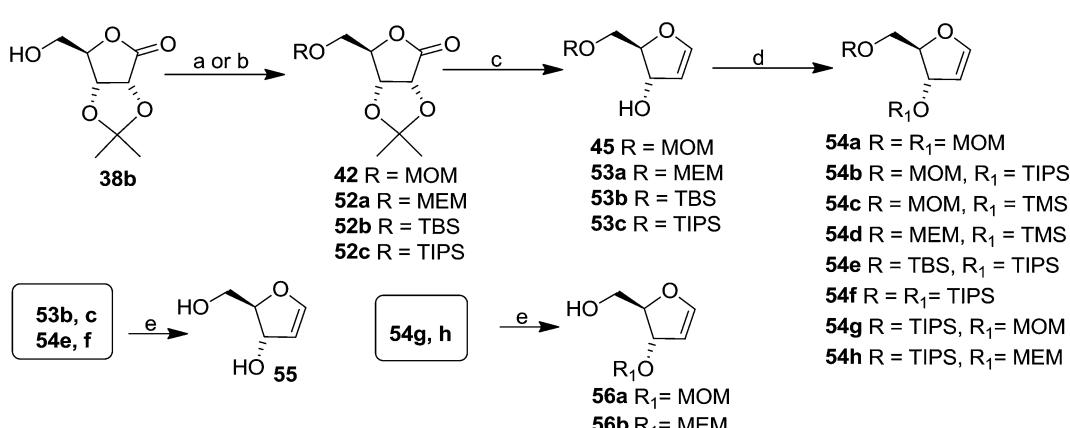
^b 2 equiv. 0.07 M THF, 25 °C, 3 h. ^c 6 equiv. 0.21 M THF, -35 °C, 20 min, then H₂O. ^d 5 equiv. 0.50 M THF, 25 °C. ^e 5 equiv. 0.25 M THF, 25 °C. ^f 5 equiv. 0.25 M THF, -20 °C → 0 °C, 1 h, then H₂O. ^g 5 equiv. 0.20 M THF, -78 °C, 15 min, then H₂O. ^h No reaction.

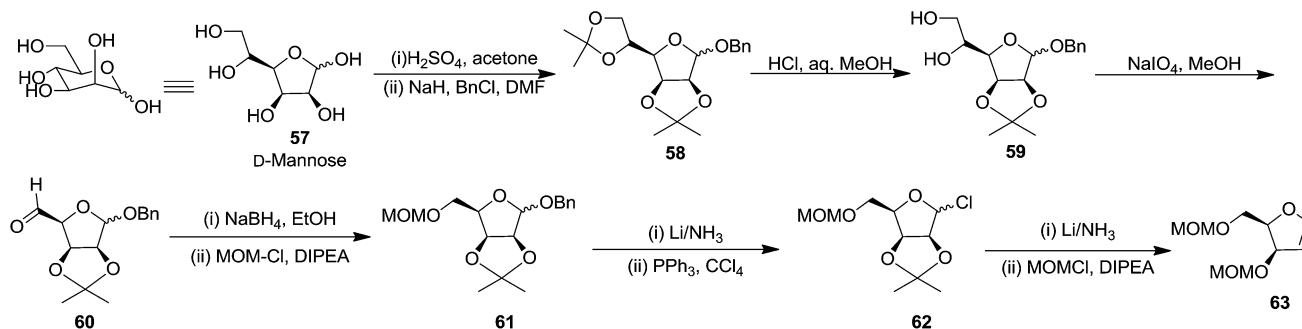
ketene acetals **49** and **51**, derived from the furanoid glycal esters (**48**, **50**) by deprotonation with LDA in a 23 vol% mixture of hexamethylphosphoric triamide (HMPA) in THF or in 100% THF at -78 °C followed by silylation of enol ether with TMSCl (Scheme 8). Protected furanoid glycal **49** 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/NH₃ systems, sodium naphthalene 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*Pr₂EtN, DCM; (ii) MEMCl, *i*Pr₂EtN, DCM; (b) to obtain **52b** and **52c**: (i) TBSCl, imidazole, DMF; (ii) TIPSCl, imidazole, DMF; (c) ref. 4, 18 and 19; (d) ref. 20a; (e) ref. 20b.



Scheme 11

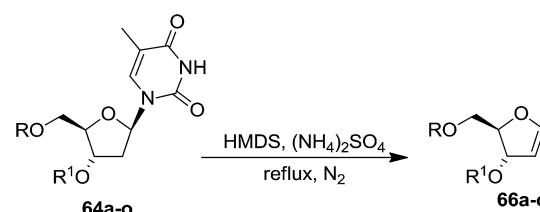
isopropylidene-D-mannofuranose was benzylated with $BnCl$ in the presence of NaH in dry DMF to afford benzyl protected compound **58** in good yield. The globally $-OH$ protected compound **58** was treated with HCl in aq. $MeOH$ to form diol **59** in 92% yield, which on treatment with $NaIO_4$ in 3 : 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*-(2S,3R)-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

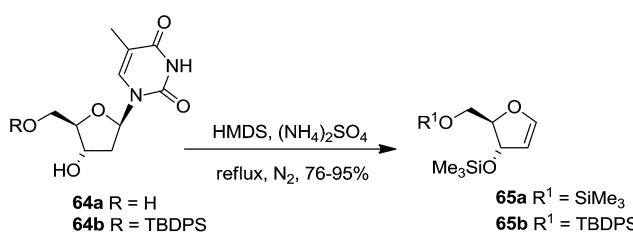


Scheme 13

Table 3 Product yields for furanoid glycals

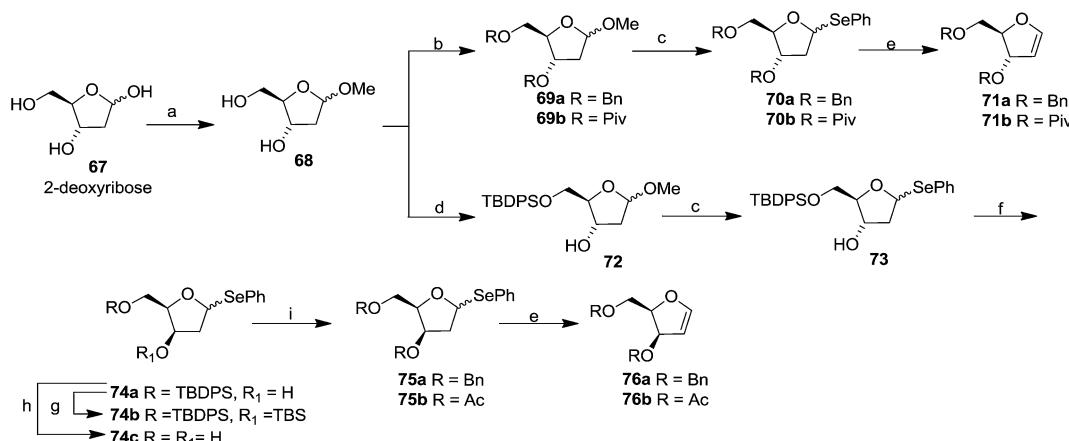
Thymidine	Glycal	R	R ¹	Yield (%)	Yield (%) from 64a ^a
64a	66a	H	H	80	80(1)
64b	66b	TBDPS	H	91	70(2)
64c	66c	TBS	H	74	53(2)
64d	66d	Tol	H	52	38(2)
64e	66e	TBS	TBS	69	47(2)
64f	66f	TBDPS	TBDPS	80	76(2)
64g	66g	Tol	Tol	No glycal	No glycal
64h	66h	TBS	TBDPS	79	55(3)
64i	66i	TBS	Tol	No glycal	No glycal
64j	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**.



Scheme 12





Scheme 14 Reagents and conditions: (a) HCl/MeOH (0.05%); (b) (i) BnBr , NaH , THF (69a); (ii) PivCl , Py (69b); (c) PhSeH , BF_3 /Et₂O, DCM, -5°C (70, 73); (d) TBDPSCI /Im/DMF 72; (e) ${}^1\text{Pr}_2\text{EtN}$ /tBuOOH/Ti(O- ${}^1\text{Pr}$)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) $n\text{Bu}_4\text{NF}$, THF; (i) (i) BnBr , NaH , THF (75a), (ii) Ac_2O , py (75b).

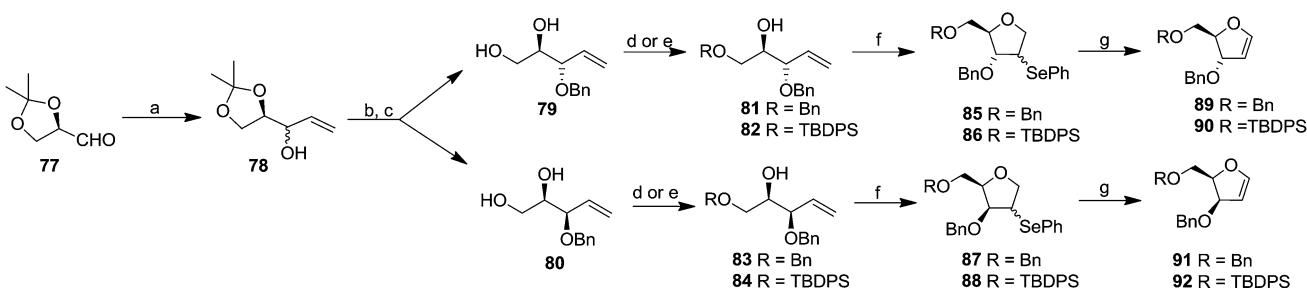
$n\text{Bu}_4\text{NF}$ led silyl deprotection to give 74c whose phenylseleno derivatives 75a and 75b were easily obtained by usual benzyl and acyl protections respectively. Oxidation followed by thermal elimination of these phenyl-2-deoxy-selenofuranosides 70a, 70b and 75a, 75b with ${}^1\text{Pr}_2\text{EtN}$ /tBuOOH/Ti(O- ${}^1\text{Pr}$)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 TBDPSCI 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

preferentially 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, ${}^1\text{Pr}_2\text{EtN}$, Ti(O- ${}^1\text{Pr}$)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.

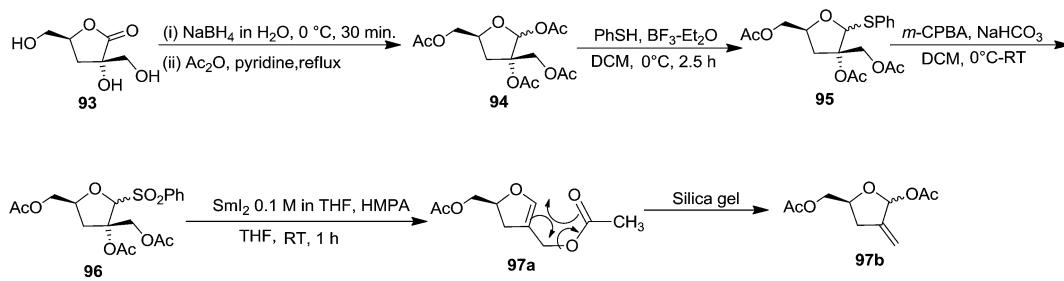
They further extended their work to synthesize differently protected *erythro* and *threo* furanoid glycals by oxidative elimination of 1-phenylselenenyl furanosides and 2-phenylselenenyl-1,4-anhydroalditol in the presence of *t*BuOOH, Ti(O- ${}^1\text{Pr}$)₄ and ${}^1\text{Pr}_2\text{EtN}$ system.²⁶

In 1995 Florent and co-workers reported the synthesis of 2'-*C*-acetoxymethylfuranoid glycal 97a by reductive elimination 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 -Et₂O/DCM gave thiophenyl glycoside 95. Its oxidation with *m*-CPBA produced phenyl sulfone 96 whose reductive selenation 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: TBDPSCI , imidazole, DMF; (f) *N*-PSP, CSA, DCM; (g) *t*BuOOH (2.5 equiv.), ${}^1\text{Pr}_2\text{EtN}$ (1.7 equiv.) and Ti(O- ${}^1\text{Pr}$)₄, (1 equiv.) in DCM (48 h) or DCE (4 h), reflux.





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 glycan 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** ($\alpha/\beta = 1:1$). Its mesylation followed by *in situ* elimination of MsOH furnished ribofuranoid glycan **102a-c** (Scheme 17).

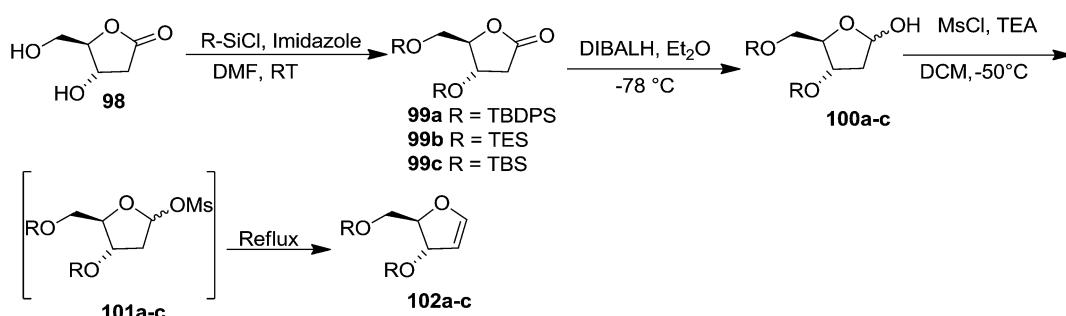
Furanoid glycan **106** was prepared by asymmetric epoxidation of allyl alcohol **103** followed by *in situ* esterification with pivaloyl chloride to give **104** (Scheme 18). Regioselective addition of

$\text{LiC}\equiv\text{CH}/\text{BF}_3\cdot\text{Et}_2\text{O}$ to **104** at low temperature (-78°C to -20°C) provided the homopropargylic secondary alcohol **105**. Treatment of **105** with $\text{Mo}(\text{CO})_6$ and trimethylamine-N-oxide in ether/Et₃N at room temperature gave **106** in 80% isolated yield (Table 4).²⁹

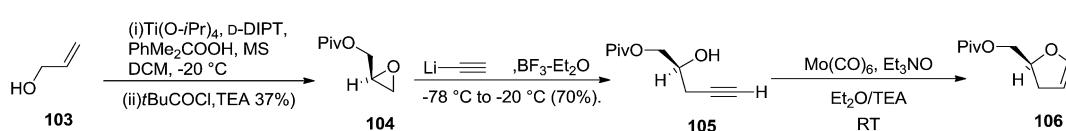
They also reported the asymmetric synthesis of alkynols having propargylic nitrogen substituents. These substrates were prepared from (*E*)-2-penten-4-yn-1-ol **107** (Scheme 19). Asymmetric epoxidation of **107** furnished **108** which on treatment with $\text{Ti}(\text{O}-i\text{Pr})_2(\text{N}_3)_2$ 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 Ac₂O and Tf₂O to obtain the respective 3-amidoalkynols **112** and **113** respectively.

The various alkynols were subjected to Mo-catalyzed alkynol cyclization to obtain furanoid glycan 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 glycan (**106**, **117**, **121**, **122**). Whereas, alkynol substrates bearing good leaving groups (*i.e.*, N₃ group) and basic groups (*i.e.*, NH₂, OR) at

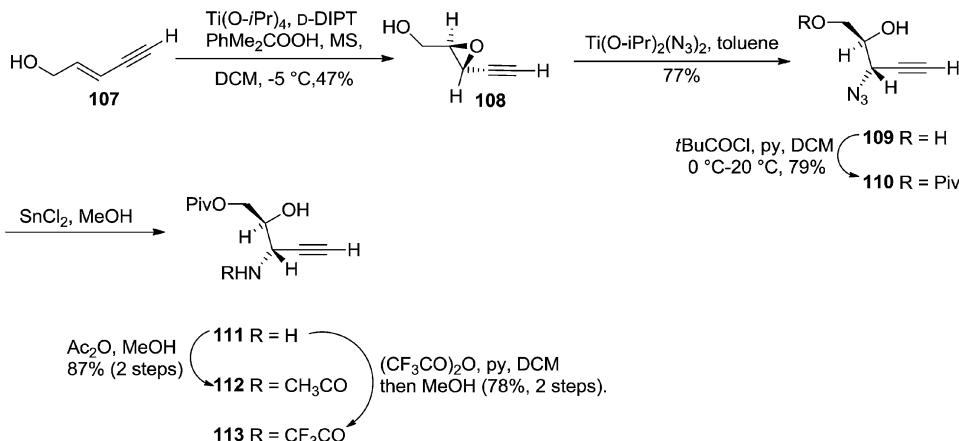


Scheme 17



Scheme 18

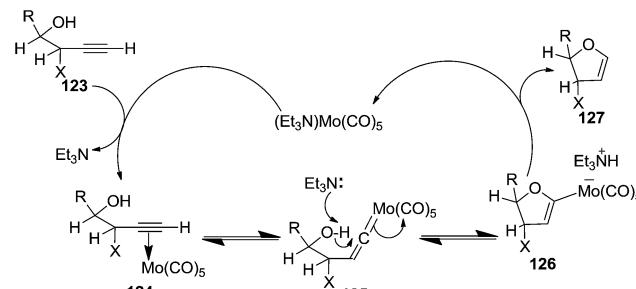




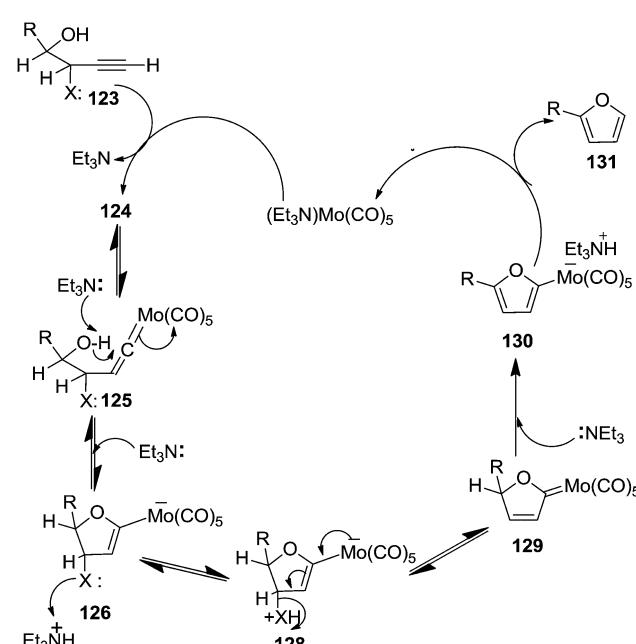
Scheme 19

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 = N3, or basic groups i.e. NH2, OR).



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

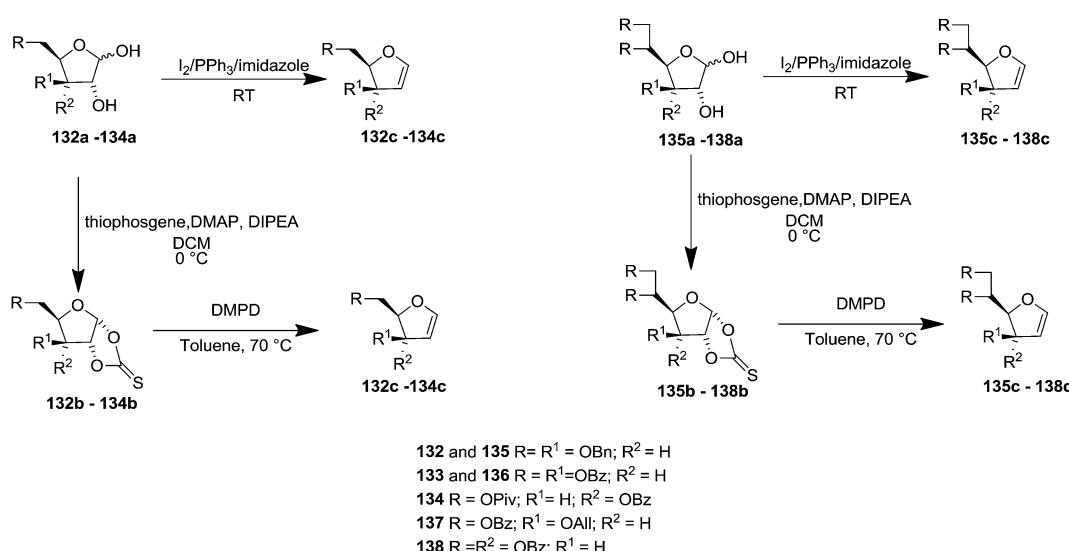
The first one referred to the Garegg-Samuelsson reaction on *vic*-diols (**132a**–**138a**) in the presence of I_2 - $PPPh_3$ -Im caused substitution followed by elimination of unstable *vic*-diiodide intermediate to the corresponding furanoid glycals (**132c**–**138c**) (Scheme 22).

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

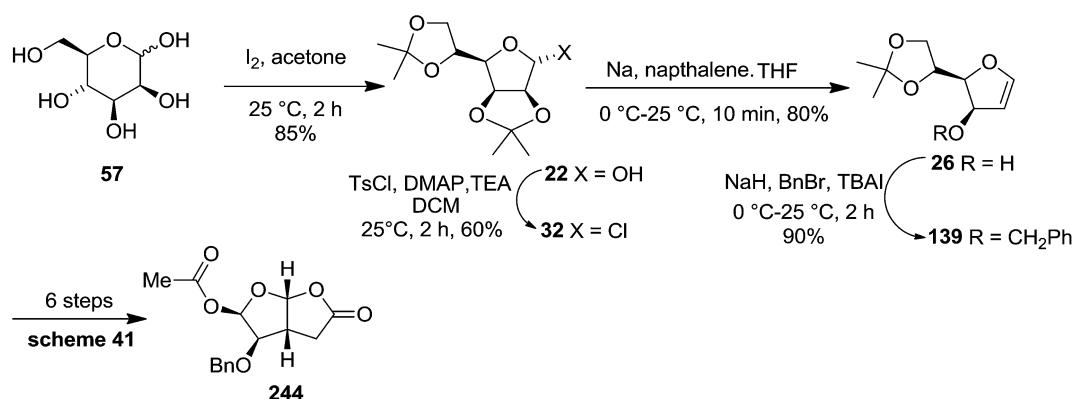
(DMPD) in dry toluene at 70 °C underwent elimination to give furanoid glycals (**132c**–**138c**) (Scheme 22).

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

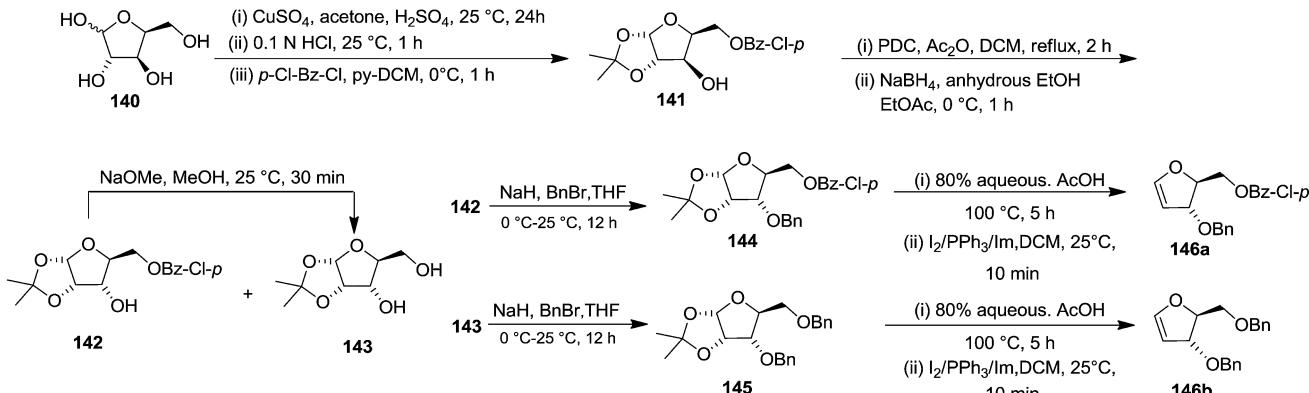


Scheme 22

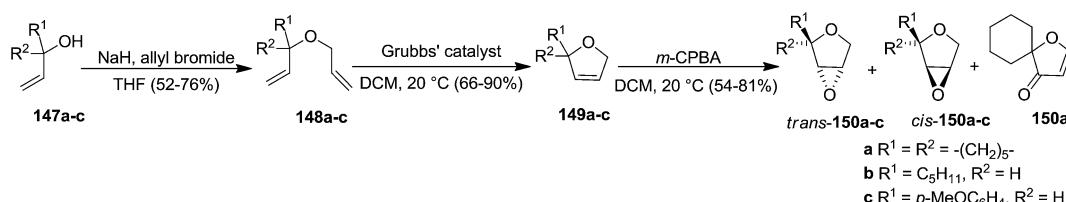


Scheme 23





Scheme 24



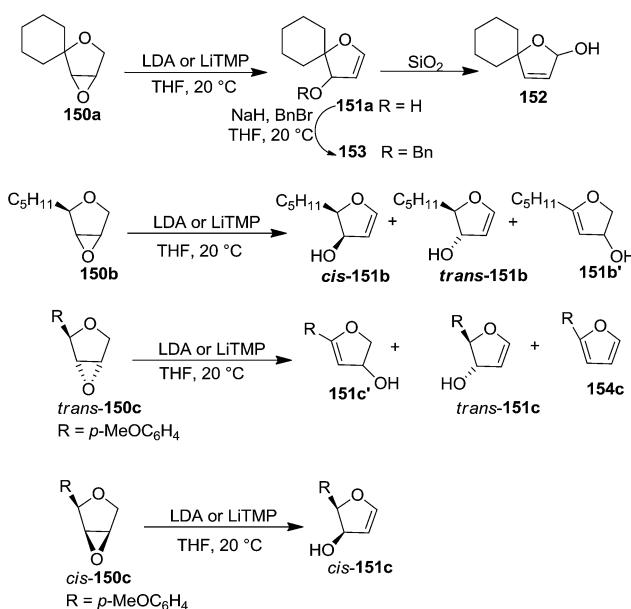
Scheme 25

of ribo furanoid glycanals 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 NaBH₄ 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-isopropylidene 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 I₂/PPh₃/Im system in dry DCM at 25 °C afforded the desired ribofuranoid glycanals **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 glycanals) utilizing ring closing metathesis 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 suppressed when free hydroxyl group in **151** was protected as a benzyl ether **153** (Scheme 26).



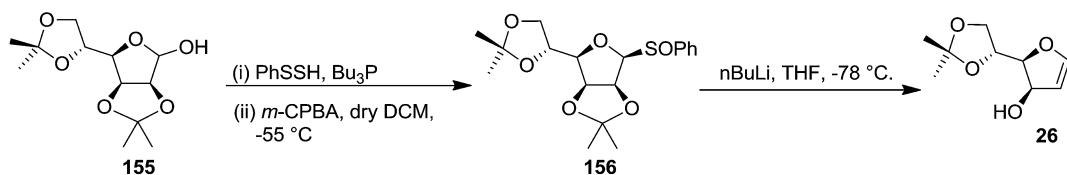
Scheme 26

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

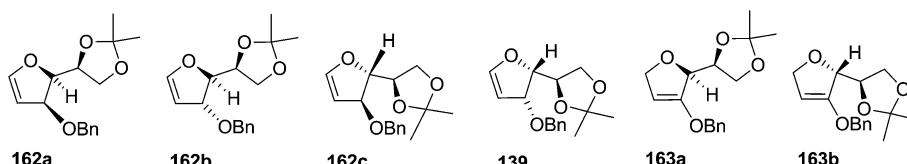
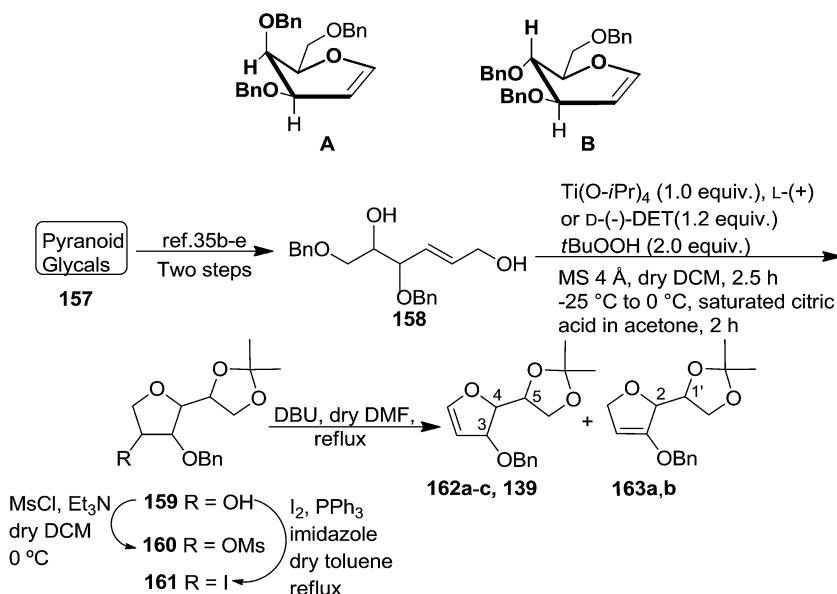


Fig. 3 Structures of furanoid glycals (162a–c, 139) and highly functionalized 2,5-dihydrofurans (163a, b).



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

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				—
2				
3				—
4				 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				—
2				—
3				
4			 139:162c = 1:0.2 from ¹ H NMR	—



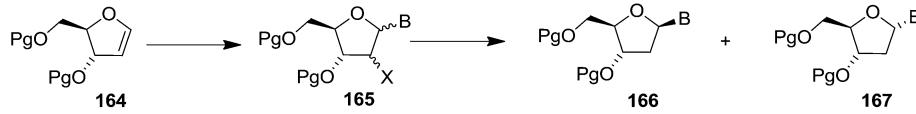
THF scaffolds (**159a–d**) were prepared from Pyranoid glycals (**157**) (3,4,6-tri-*O*-benzyl-*D*-galactal (**A**) and 3,4,6-tri-*O*-benzyl-*D*-glucal (**B**)) derived allylic alcohols (**158**) involving the intramolecular asymmetric ring opening (ARO) of the enantiomerically pure 2,3-epoxy alcohols 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 *Et₃N* 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 (*I₂/PPh₃/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

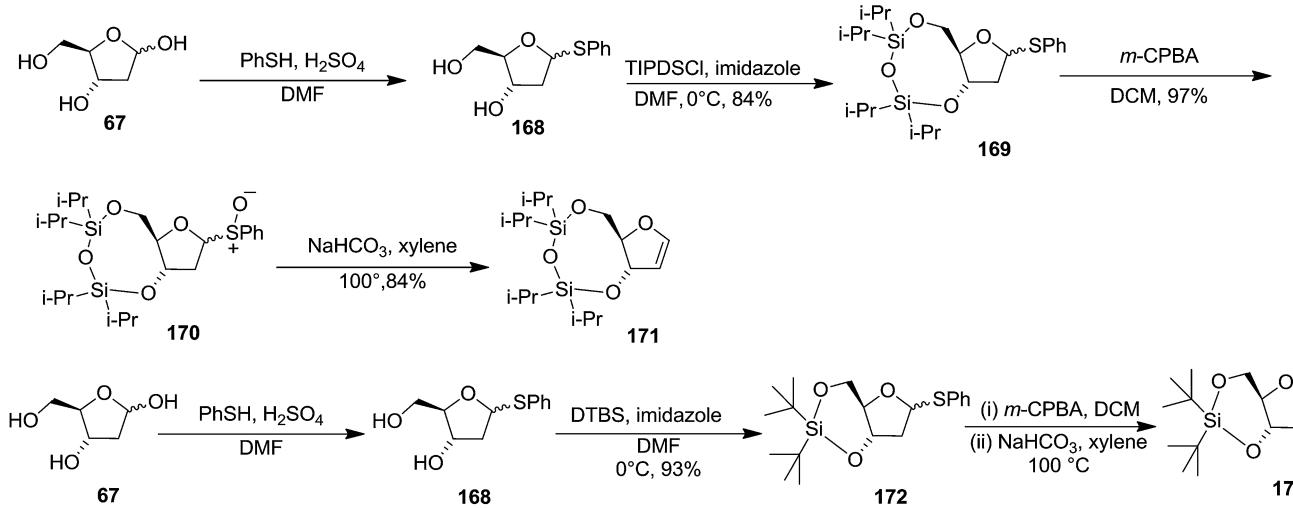
atoms at C5 adopted a relatively higher degree of antiperiplanar arrangement relative to the antiperiplanar arrangement of 4-OMs and H3. In contrast, the formation of Saytzeff product **163b** as the major product and a mixture of glycals (**162c**, **139**) as the minor product, both from **160d**, 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'-deoxy-nucleosides (**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/H₂SO₄* 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



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 synthesis³⁹ 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

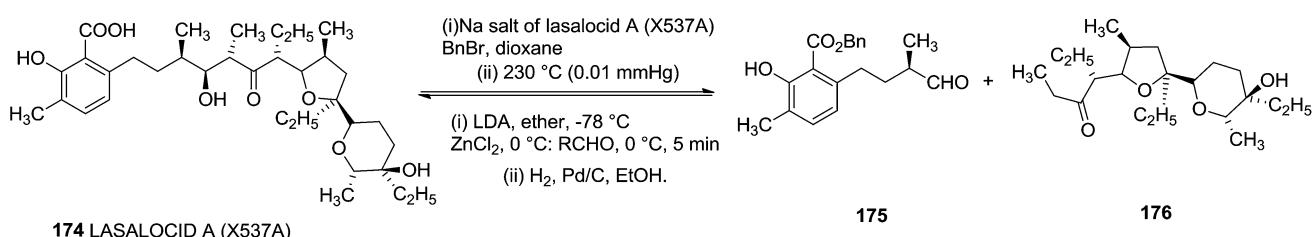
aldehyde **175** and ketone **176** available from the reverse aldol reaction of lasalocid A (X537A) **174** (Scheme 31).^{40,41}

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).

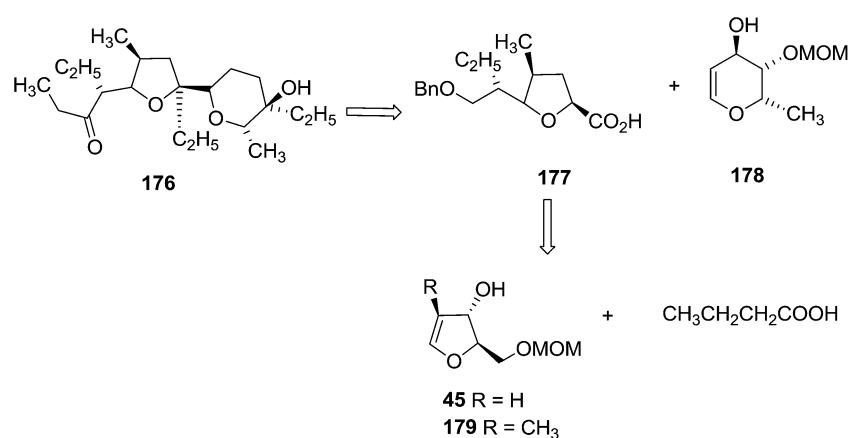
First they tried the synthesis of **176** from furanoid glycal **45** which was converted to protected furanoid glycal **49** which is described in Scheme 8,⁴ from which the isomeric mixture of acid **180** was prepared by [3,3] sigmatropic rearrangement at 35 °C.⁴ This acid mixture **180** was converted 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).

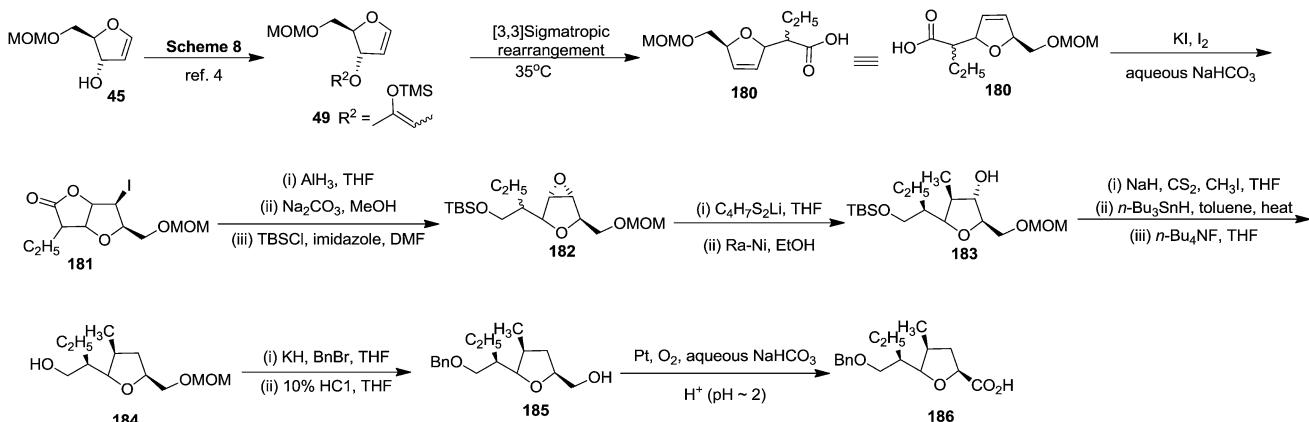
The construction of Pyranoid glycal **178** started with 6-deoxy-L-gulose **195** as shown in Scheme 35. The hydroxyl groups were differentiated as benzyl glycoside, *O*-isopropylidene, and methoxymethyl ether in compound **196**. Removal of the benzyl



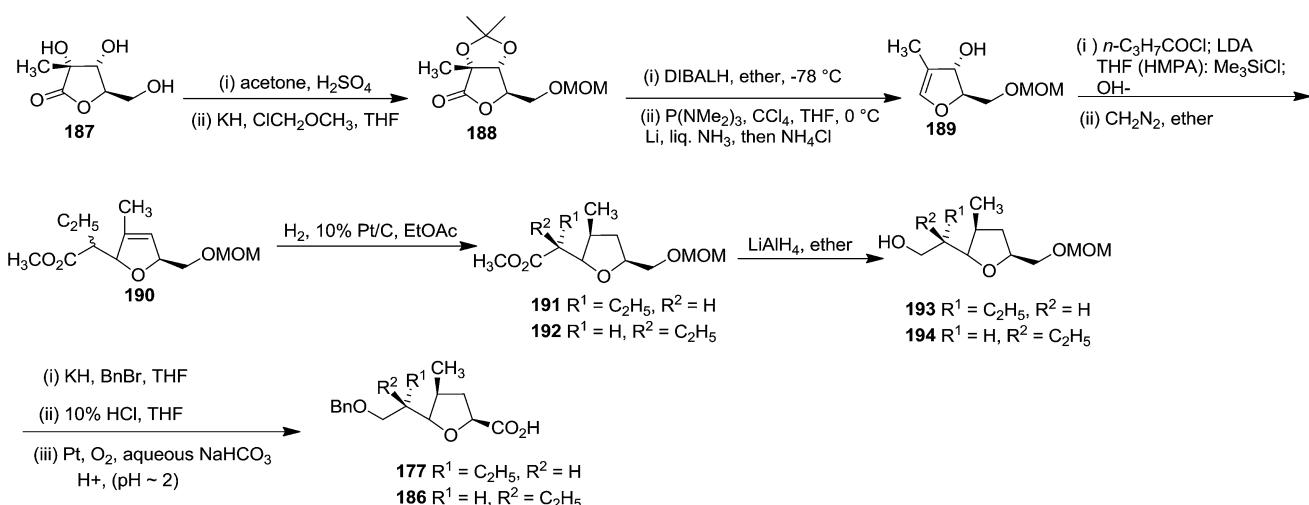
Scheme 31



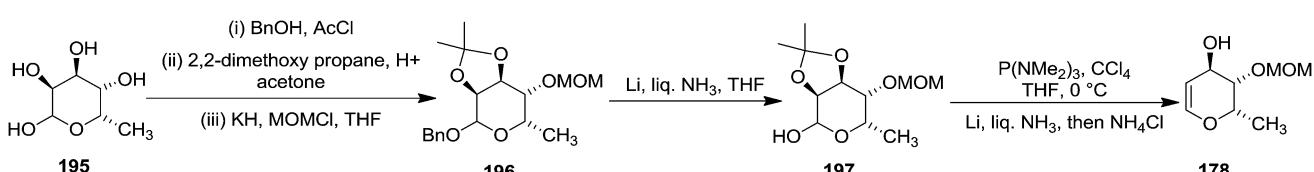
Scheme 32 Retro synthetic strategy for synthesis of ketone 176.



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).

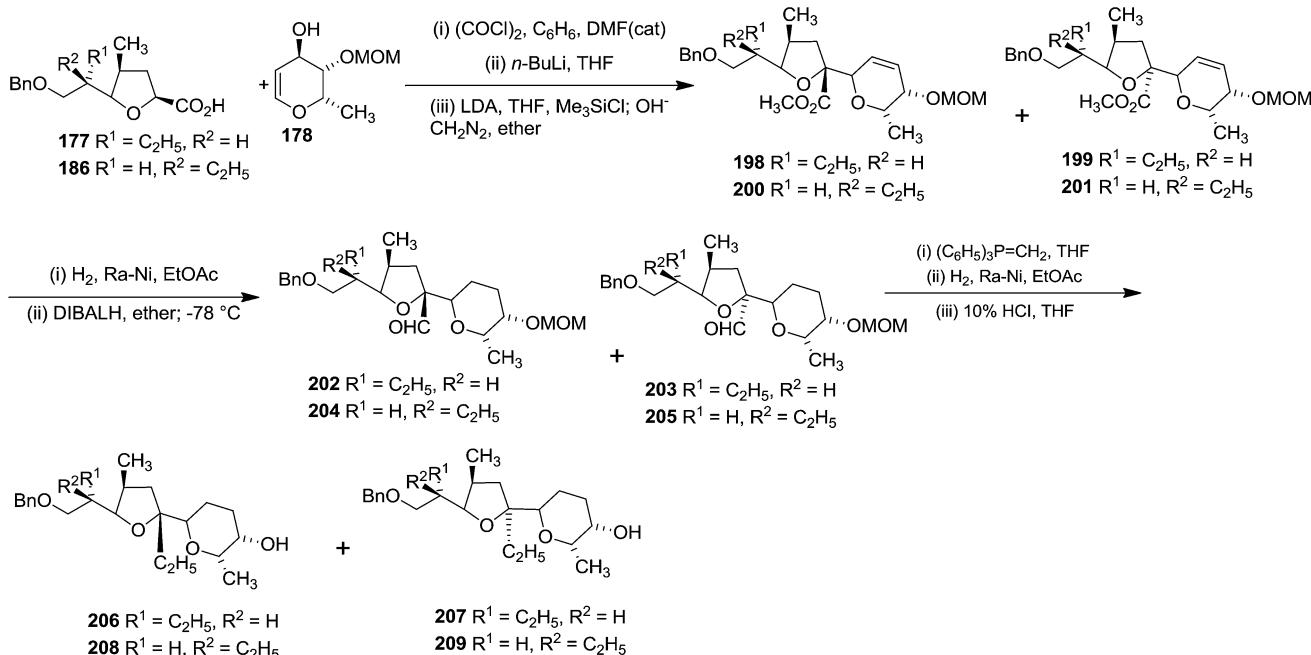
The connection of the pyranoid subunit 178 to acid 177 resulted in readily separable isomeric esters 198 and 199, while the epimer 186 afforded the isomeric esters 200 and 201. Subsequent transformation of these esters individually to alcohols 206–209 proceeded in excellent yields *via* 202–205 (Scheme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

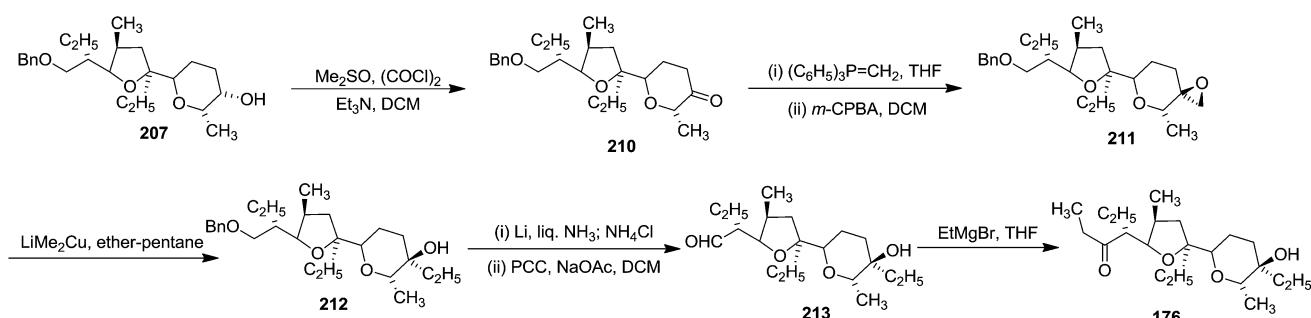
211 was the major component. Subsequent reductive cleavage of this isomer then led to the tertiary alcohol 212 which was transformed into the aldehyde 213 involving sequence of reactions like debenzylation and oxidation of the resulting primary alcohol. Finally its Grignard reaction furnished the ketone 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

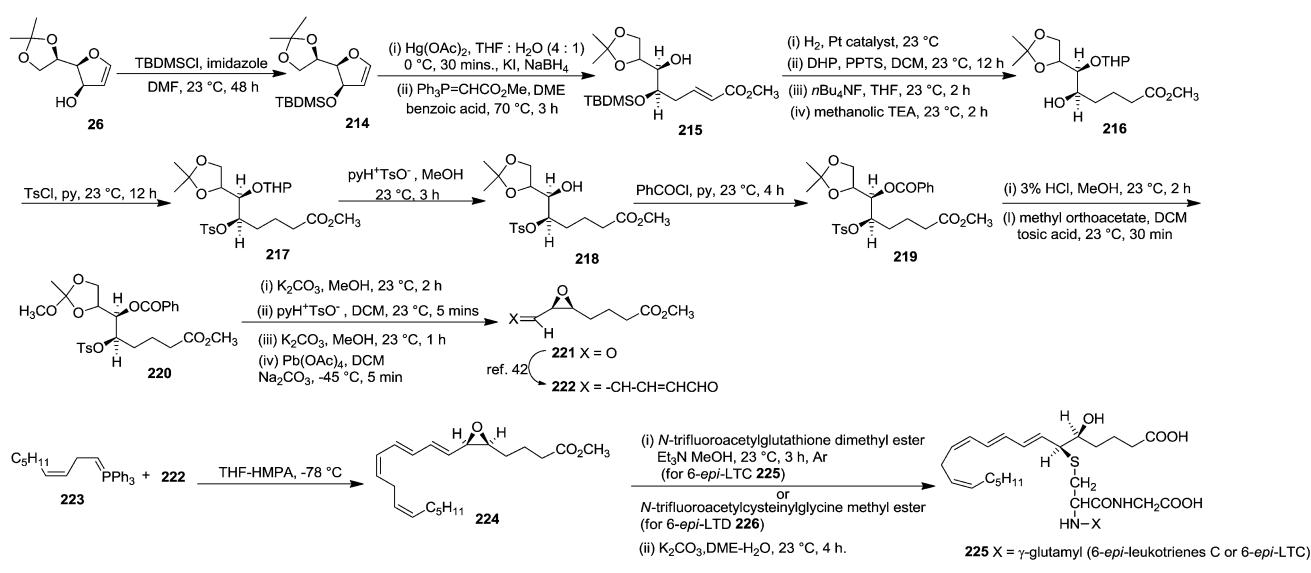




Scheme 36



Scheme 37



Scheme 38

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 K₂CO₃ 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 K₂CO₃ 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 5S,6R 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 Et₃N in a minimum quantity of methanol at 23 °C for 3 h under Ar

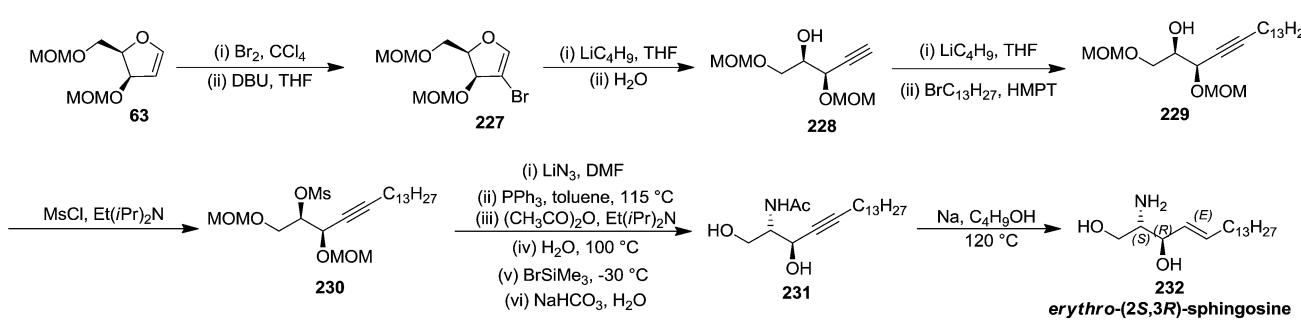
atmosphere and (ii) deprotection with K₂CO₃ in 4 : 1 dimethoxyethane-water at 23 °C for 4 h to afford **225**.

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

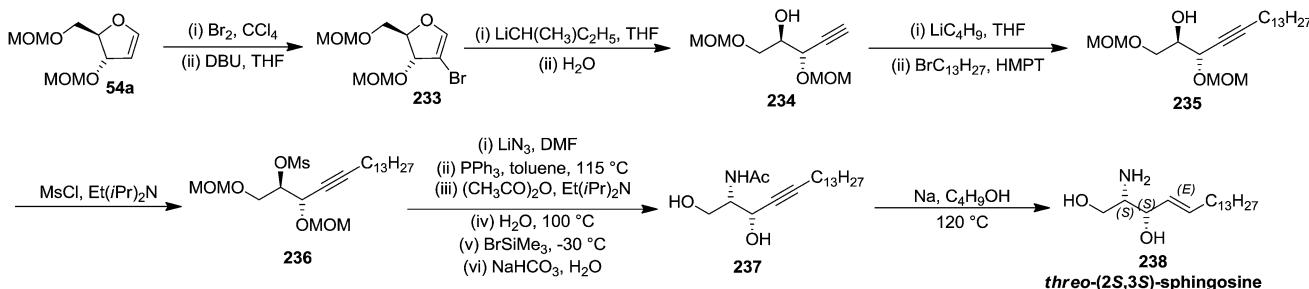
Schlosser and coworkers described the synthesis of *threo*-furanoid glycal **63** (Scheme 11), *erythro* furanoid glycal **54a** (Scheme 10)^{20a} and utilized them as key intermediates for synthesis of *erythro*-(2S,3R)-sphingosine **232** (Scheme 39) and *threo*-(2S,3S)-sphingosine **238** (Scheme 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 Rh₂(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 NaIO₄, the resulting aldehyde was methylated to produce **241** in 63% combined yield. Its Swern oxidation produced ketone **242** in 79% yield, which on MeSO₃H mediated cyclization at 0 °C furnished bicyclic **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 (+)-myriocene **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

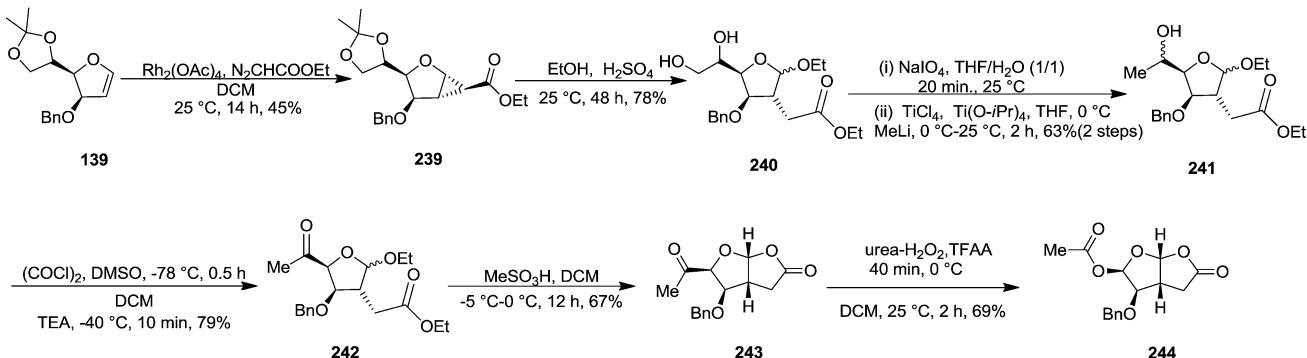


Scheme 39

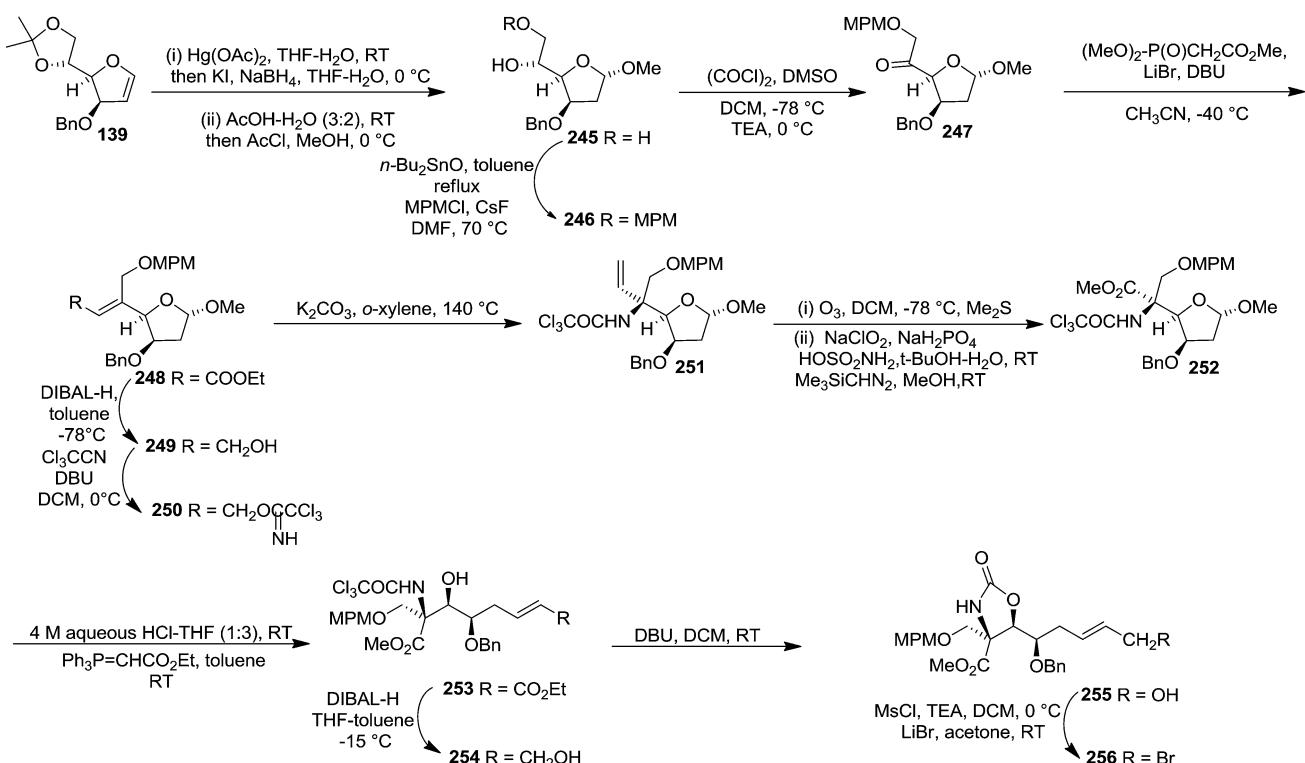


Scheme 40





Scheme 41

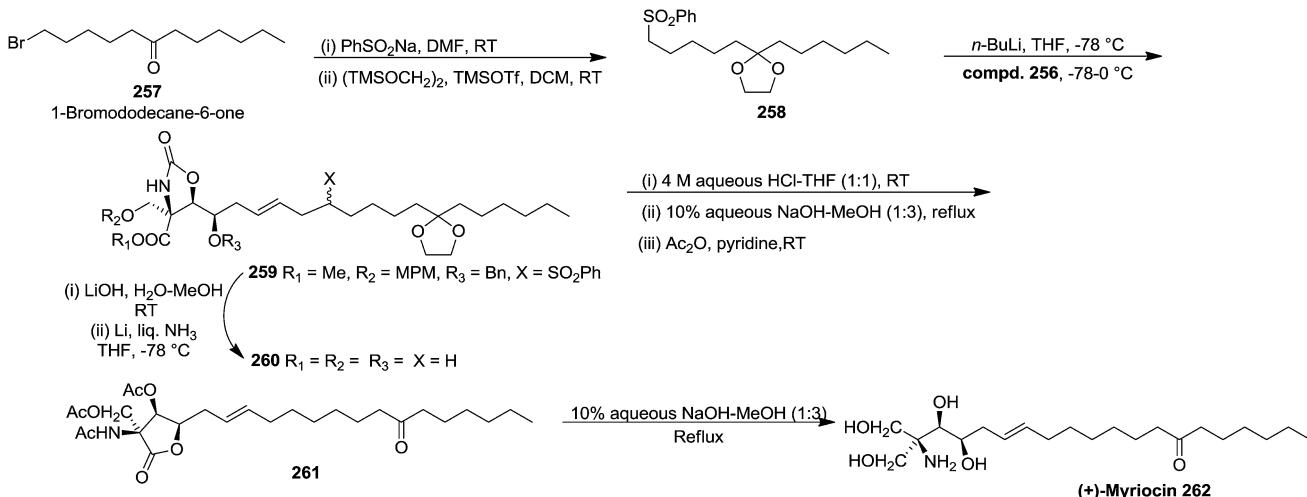


Scheme 42

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 $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ 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



Scheme 43

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

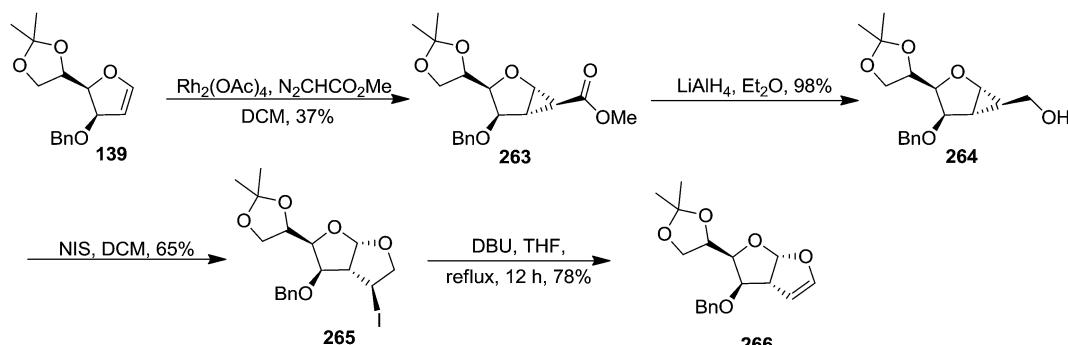
In 2007, Chandrasekharan and coworkers developed a methodology for the construction of fused perhydrofuro[2,3-*b*]pyran/furan by using NIS mediated ring opening and cyclization of 1,2-cyclopropanated sugar derivatives, derived from pyranoid and furanoid glycals. They successfully applied this methodology to the synthesis of fused perhydrofuro[2,3-*b*]pyran/furan- 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 $\text{Rh}_2(\text{OAc})_4$ 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

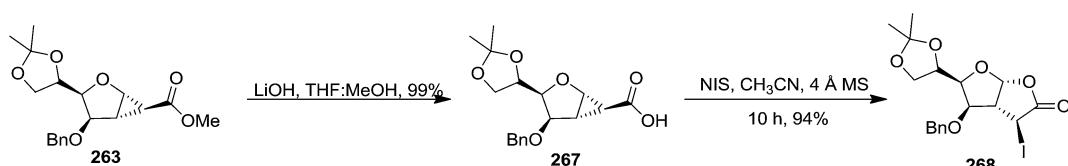
opening and cyclization reaction to furnish perhydrofuro[2,3-*b*]furan derivative 265 in 65% yield as a mixture of diastereomers (9 : 1). The mixture was subjected to dehydrohalogenation with DBU (THF, reflux, 12 h) to obtain the corresponding furofuryl glycal 266 in 78% yield (Scheme 44).

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

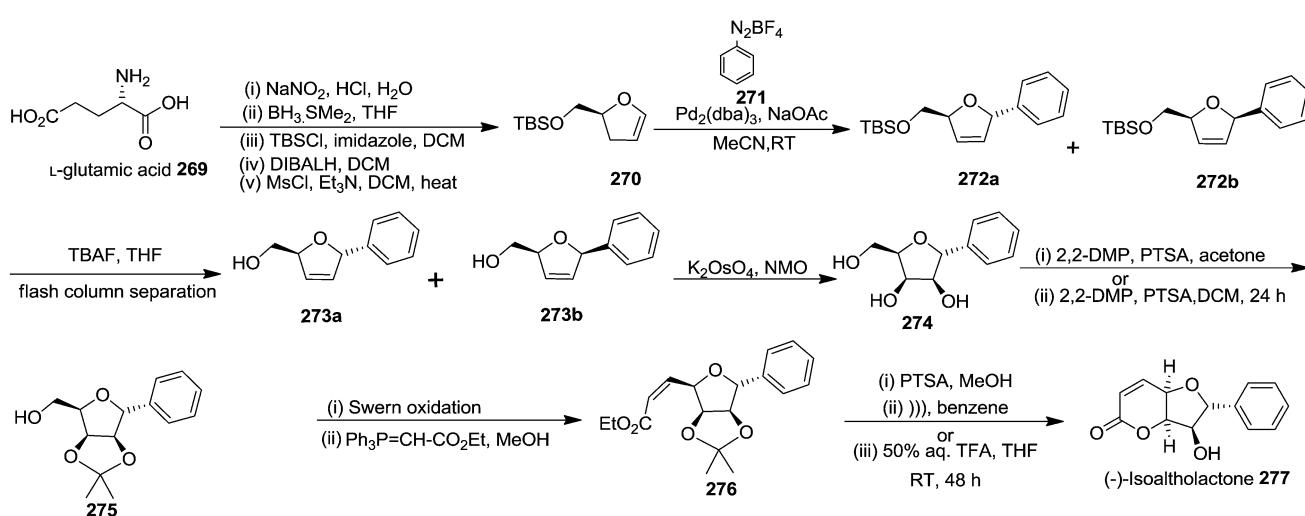


44) by utilizing Heck–Matsuda arylation with benzenediazonium tetrafluoroborates as the key step.⁴⁵ After performing several trial and error experiments, they achieved the best condition for Heck–Matsuda arylation of enoether 270 with benzenediazonium tetrafluoroborates 271 in the presence of 4 mol% of $Pd_2(dba)_3$, to afford the phenyldihydrofurans 272a and 272b in 90% yield as a 94 : 06 inseparable diastereomeric 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

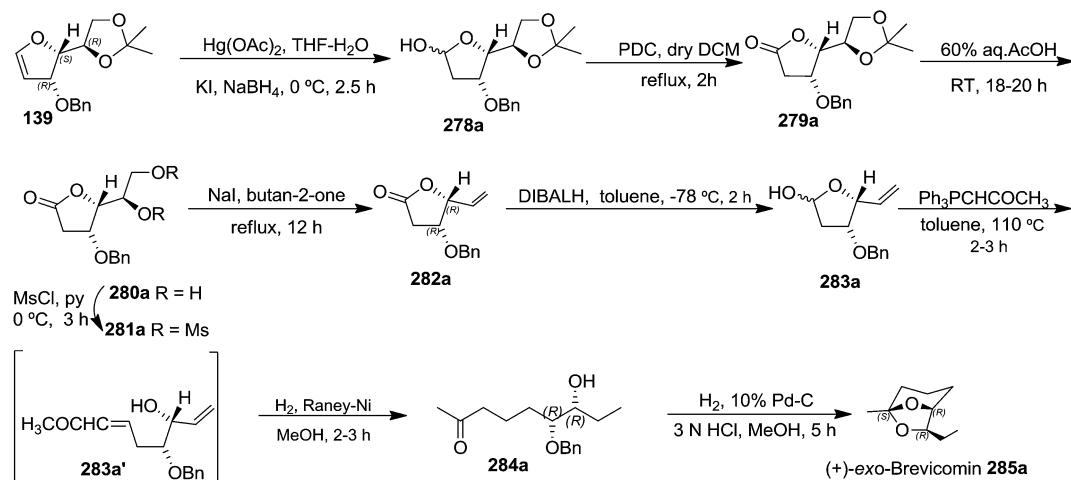
with catalytic PTSA in methanol followed by sonication to obtain (–)-isoaltholactone 277 in 70% yield (2 steps). However, when *cis*-enoate 276 was treated with an aqueous solution of trifluoroacetic acid for 48 h at room temperature, the (–)-isoaltholactone 277 was obtained in 80% yield (Scheme 46).

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}

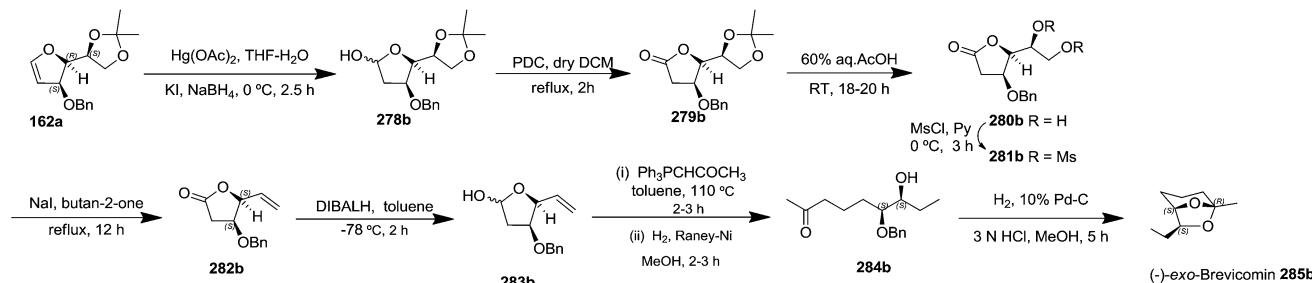
The total synthesis of (+)-*exo*-brevicomin 285a was initiated from furanoid glycal 139 (1,4-anhydro-2-deoxy-5,6-O-isopropylidene-3-*O*-benzyl-*D*-arabino-hex-1-enitol) (Scheme 47), which was converted into 278a by oxymercuration–demercuration sequence in 98% yield. The anomeric OH was oxidized with



Scheme 46



Scheme 47



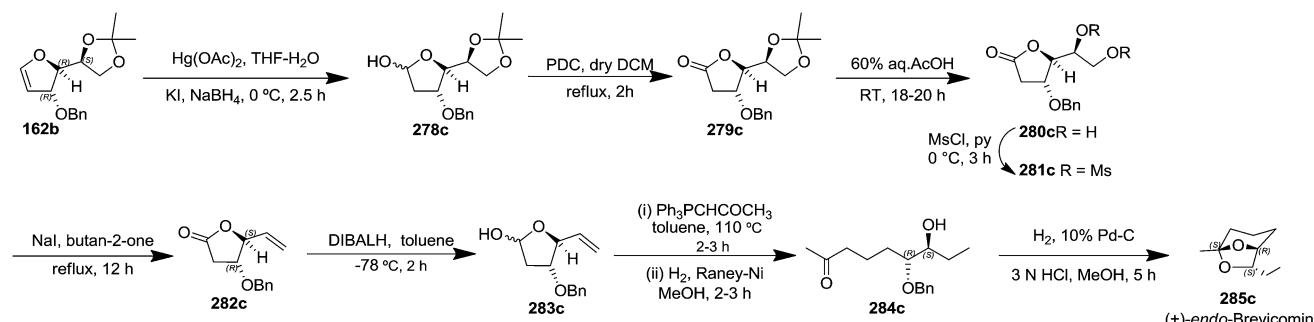
Scheme 48

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 $\text{Ph}_3\text{PCHCOCH}_3$ 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 O[–]Bn 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).

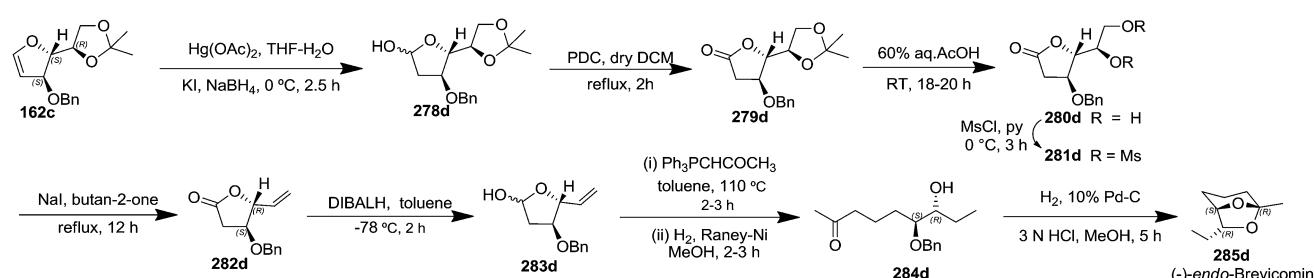
After having completed the total synthesis of (+)-*exo*-brevicomin **285a** from furanoid glycal **139**, the similar reaction

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-ribio-hex-1-enitol) (Scheme 49) and (–)-*endo*-brevicomin **285d** from **162c** (1,4-anhydro-2-deoxy-5,6-O-isopropylidene-3-O-benzyl-D-ribio-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 tBuOH : H₂O 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

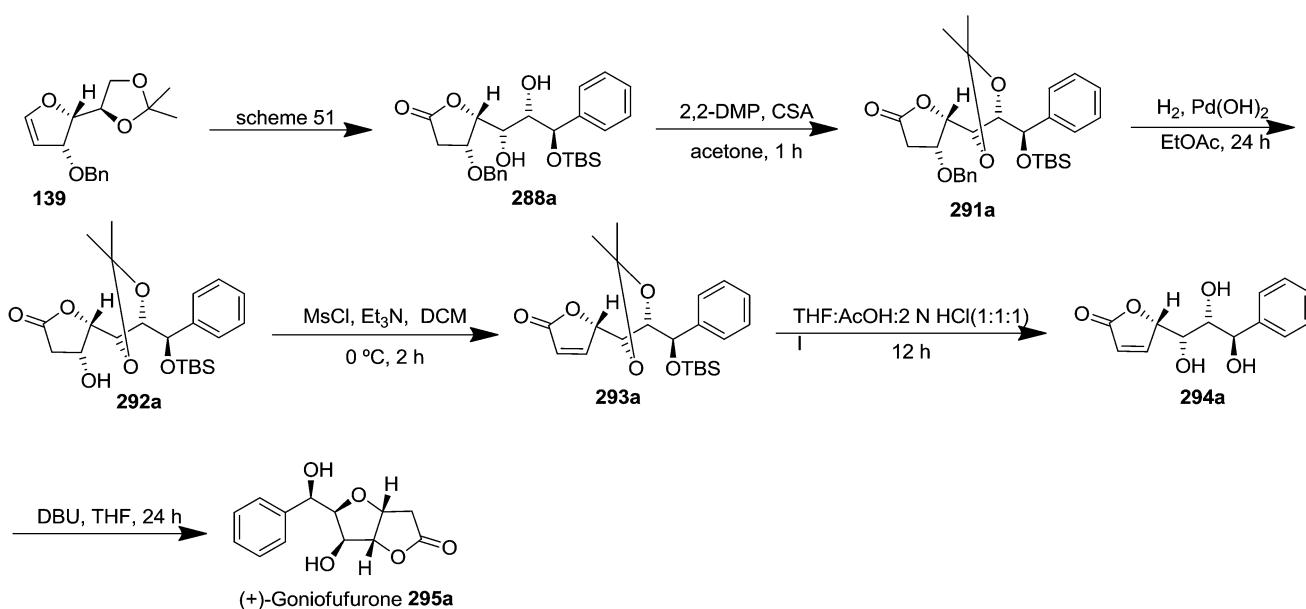
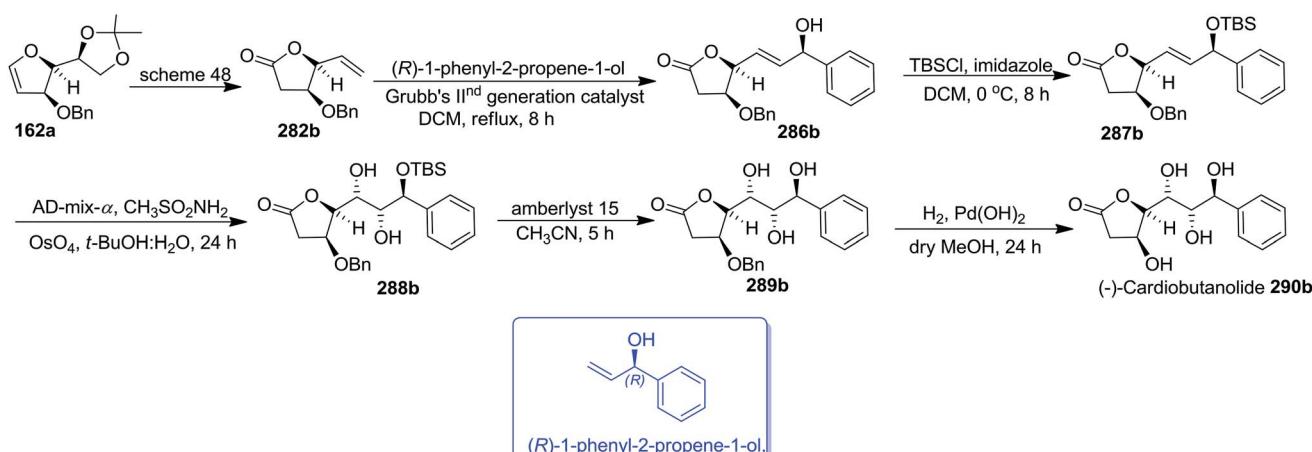
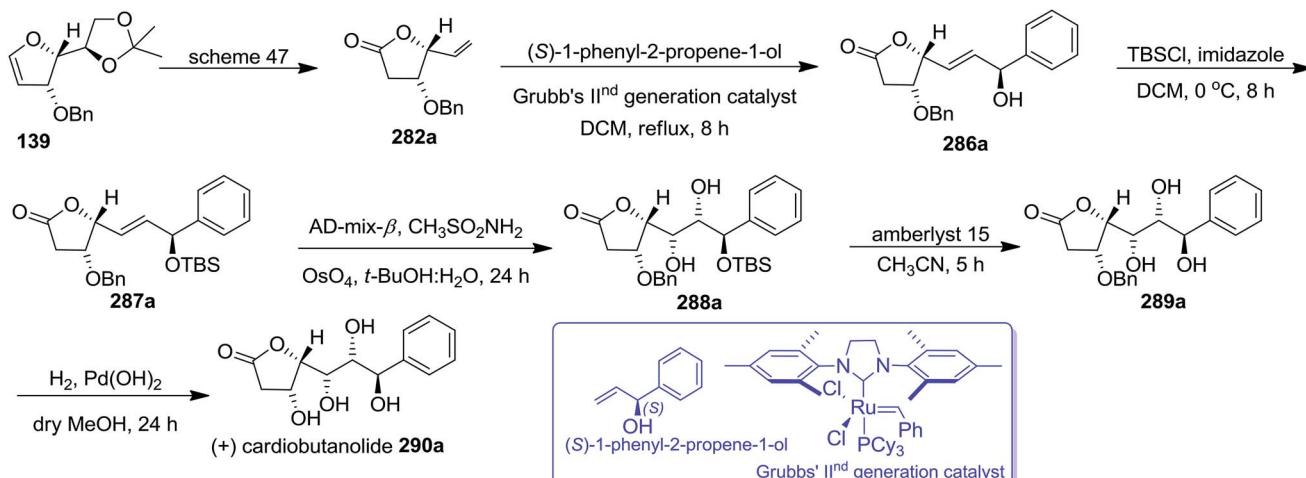


Scheme 49



Scheme 50





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 Grubbs'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 : H₂O 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-Et₃N 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 (+)-goniofuranone **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 OsO₄ 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 NaBH₄ 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*Bu₃SnH 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).

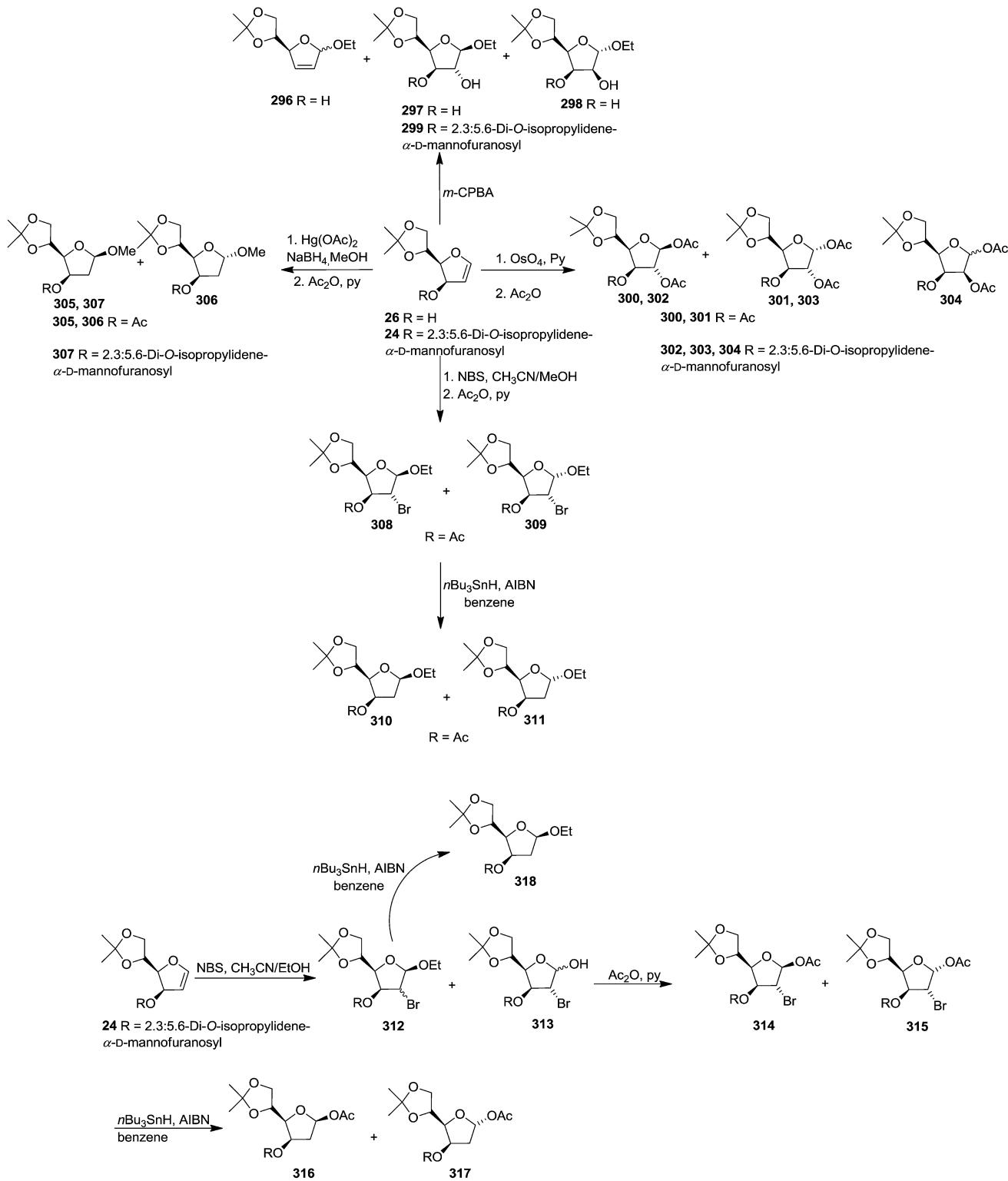
In 1987, Dax *et al.* demonstrated the reaction of acetyl hypofluorite (CH₃CO₂F) with pyranoid and furanoid glycals and they observed that more stereospecific reactions took place with furanoid glycals. Treatment of 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-D-arabino-hex-1-enitol^{16,19} **26** or 1,4-anhydro-2-deoxy-5-*O*-methoxymethyl-D-*erythro*-pent-1-enitol⁴ **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 benzylxy 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.

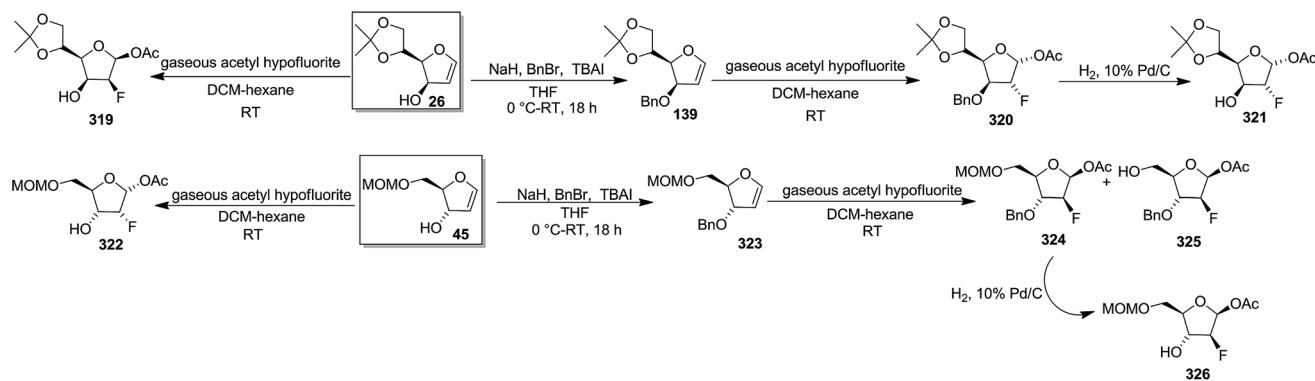
In 1987, Leblanc *et al.* discussed a new and efficient method for the preparation of 2-deoxy-2-aminoglycosides in high yields by stereoselective [4+2] cycloaddition reaction of dibenzyl azodicarboxylate (BnO₂C-N=N-CO₂Bn) on the appropriate glycals (Scheme 56, Table 7).⁴⁸ Irradiation of glycals (**327**, **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



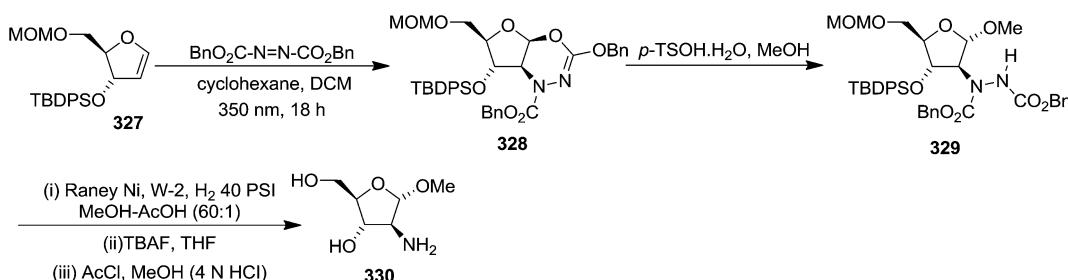
Scheme 54

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



Scheme 55

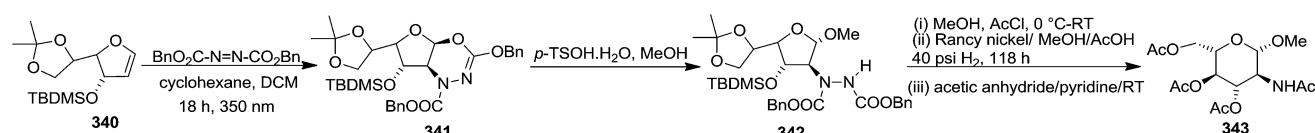


Scheme 56

Table 7 Preparation of 2-deoxy-2-aminoglycosides

Glycal	[4+2]adduct	Glycoside	Free amine
TBDPSO-	TBDPSO-	TBDPSO-	HO-
TBDMSO-	TBDMSO-	TBDMSO-	HO-
OTBDMS-	TBDMSO-	TBDMSO-	HO-

^a The hydrogenolysis was performed on the free diol obtained by desilylation of compound 332 (*n*-Bu₄NF 10 equiv, AcOH 3 equiv, THF, 90%).



Scheme 57



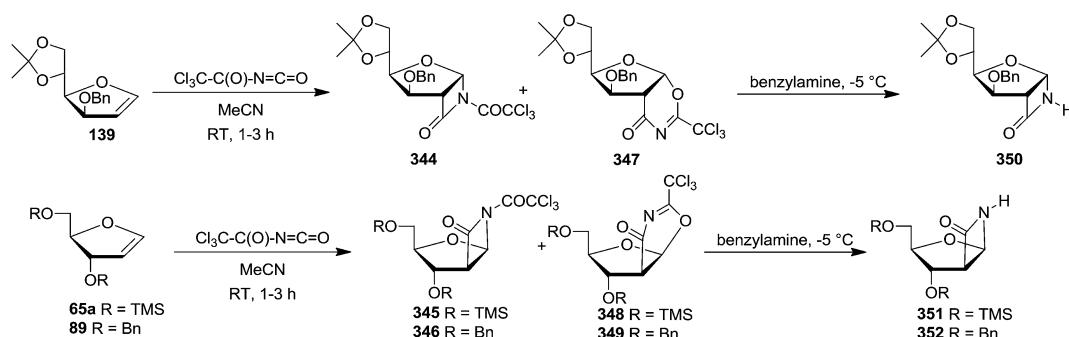
In 1993, Chmielewski *et al.* showed [2+2] cycloaddition of trichloroacetyl isocyanate to furanoid glycals. Here, the preferential attack of the reagent to the substrate was governed by the stereochemistry of the C-3 substituent. They selected furanoid glycals **139**, **65a** and **89** which on treatment 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-glucosidic configuration for **350** and β -D-arabinosidic 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**

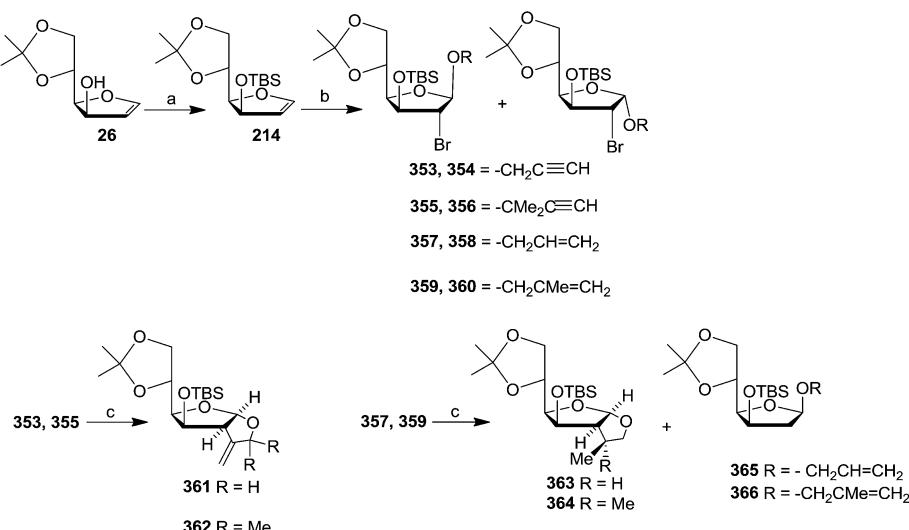
respectively as major products and **354**, **356**, **358** and **360** as minor products. The crucial regio- and stereo-selective intramolecular C–C bond formation on **353**, **355**, **357** and **359** was efficiently achieved by treating each with a catalytic amount of *n*Bu₃SnCl and AIBN in the presence of NaBH₃CN 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 cyclizations, 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).⁵¹

4.3. Wittig rearrangement

Gesson *et al.* studied⁵¹ 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



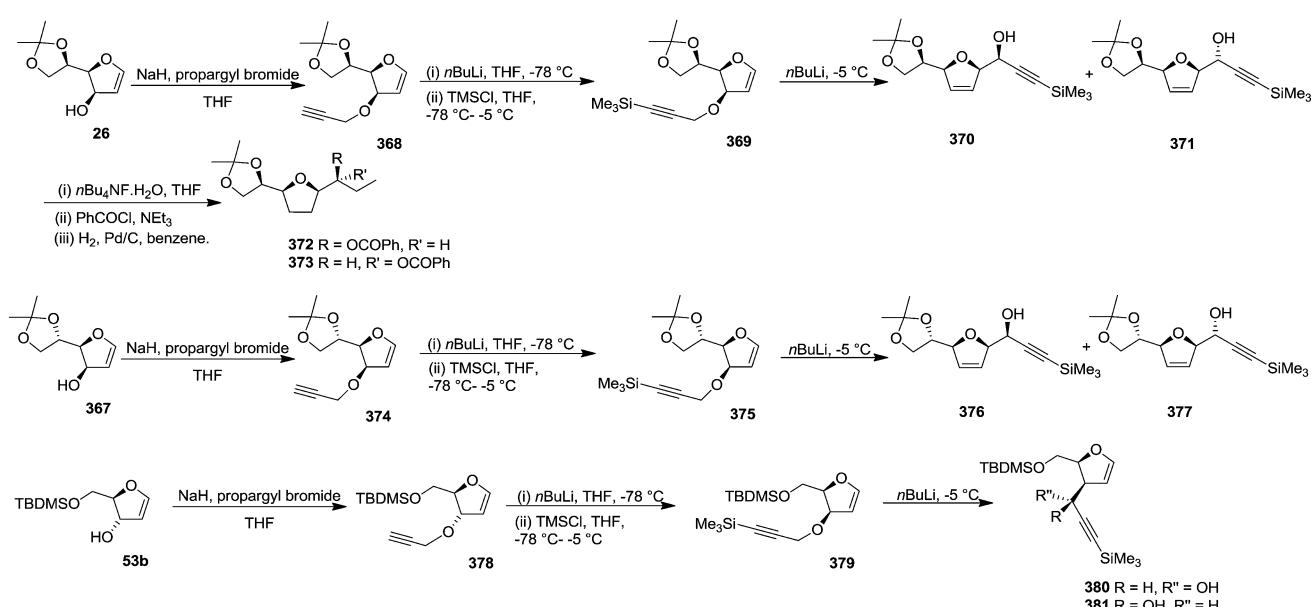
Scheme 59 Reagents and conditions: (a) TBSCl, imidazole, DMF, 83%; (b) NBS, 10 equiv. 2-propyn-1-ol (for **353**, **354**), 2-methyl-3-butyn-2-ol (for **355**, **356**), 2-propen-1-ol (for **357**, **358**), and 2-methyl-2-propen-1-ol (for **359**, **360**) respectively; (c) *n*Bu₃SnCl, AIBN, NaBH₃CN, *t*BuOH, reflux.



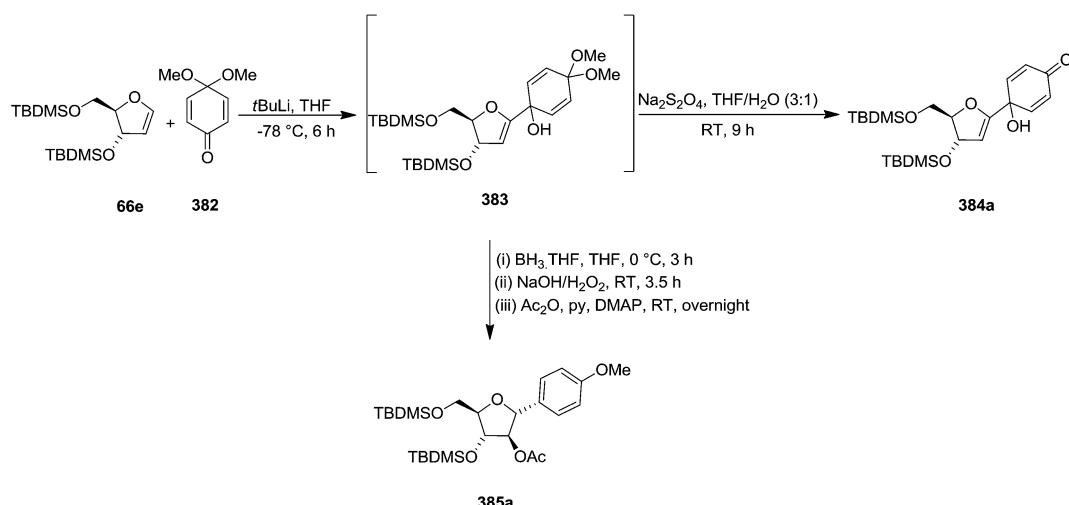
–78 °C followed by addition of TMSCl (1.1 eq., –78 °C to –5 °C) afforded 369, 375, 379 respectively. These trimethylsilylpropargyl ethers of furanoid glycals 369, 375, 379 were used in a one-pot [2,3]-Wittig rearrangement by addition of a further 1.1 eq. of *n*BuLi at –5 °C. The glycal derivative 369, 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/H₂O₂ and acylation to obtain 2'-acetate 385a in an 40% overall yield from glycal 66e (Scheme 61).

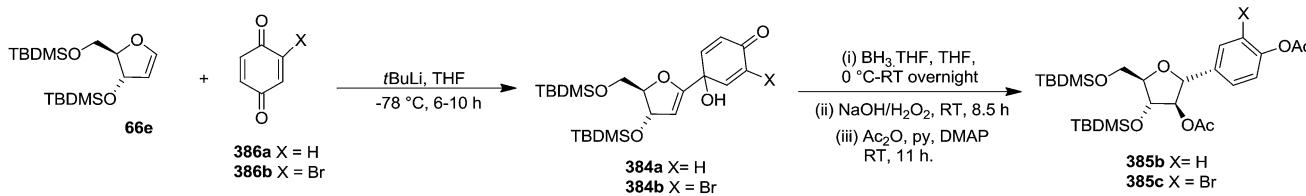


Scheme 60



Scheme 61





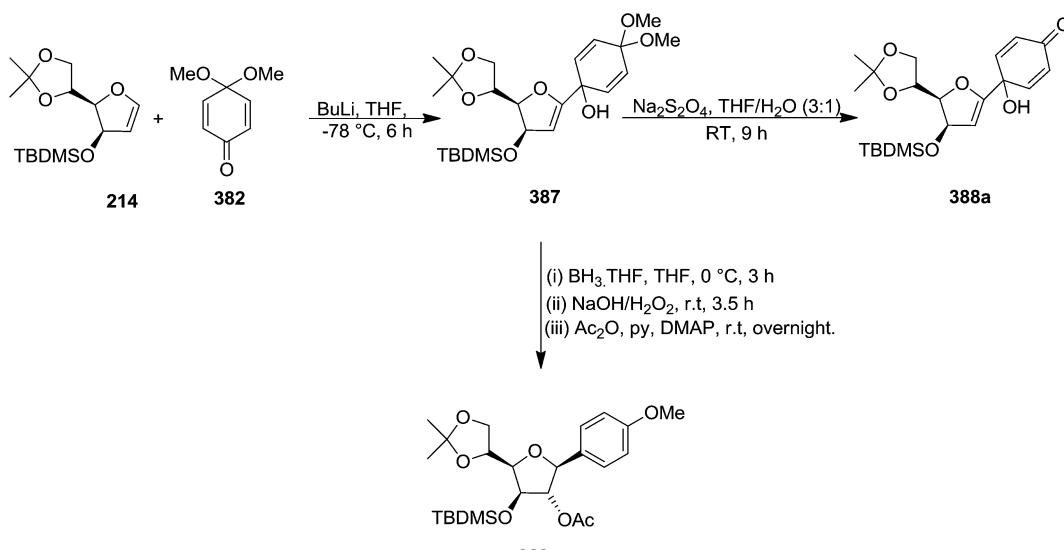
Scheme 62

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).

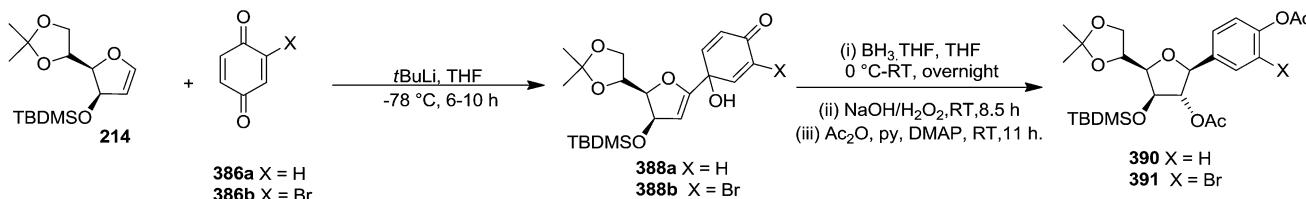
They have also reported the synthesis of C-1 aryl glucofuranosides **389**, **390**, **391** in good yields from furanoid glycal **214**, by utilizing same reaction sequence (Schemes 63 and 64).

4.5. Metal mediated amination

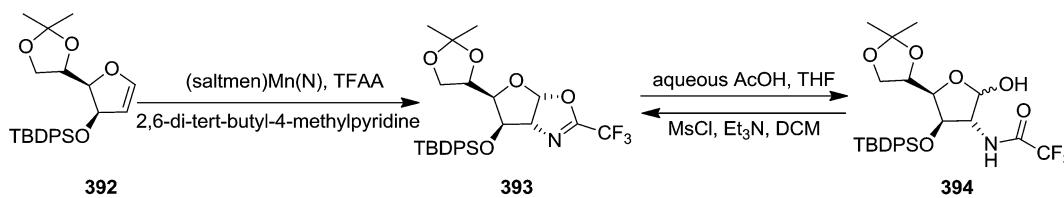
Carrier and group have synthesized stereoselectively 2-amino saccharides through metal-mediated amination of glycal substrates. They studied this reaction on differently protected pyranoid and furanoid glycals by utilizing (saltmen)Mn(N) and TFAA to transfer CF_3CON unit to electron rich silyl enol ethers.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



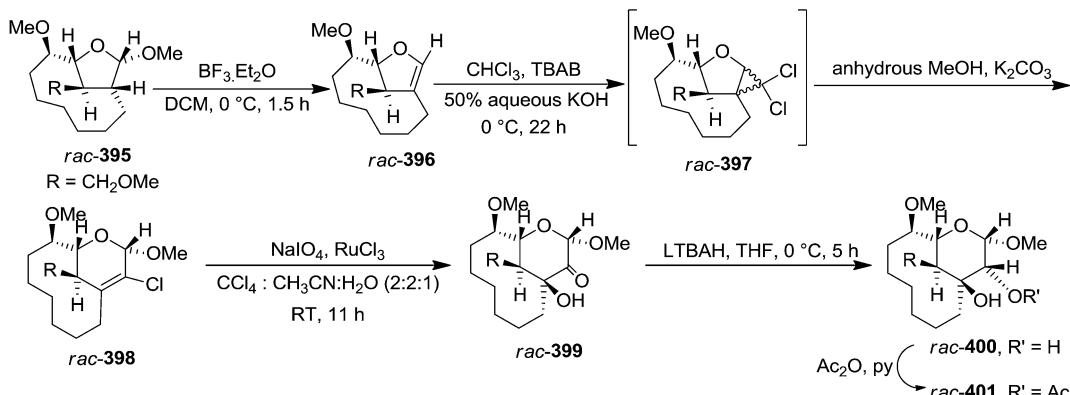
Scheme 63



Scheme 64



Scheme 65



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 $\text{BF}_3\cdot\text{Et}_2\text{O}$ in DCM in 95% isolated yield. Treatment of *rac*-396 with 50% aq. KOH in the presence of catalytic amounts of $n\text{Bu}_4\text{NBr}$ 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-2H-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 activities⁵⁵ and potential use as antiviral^{56,57} and antineoplastic⁵⁸ 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.

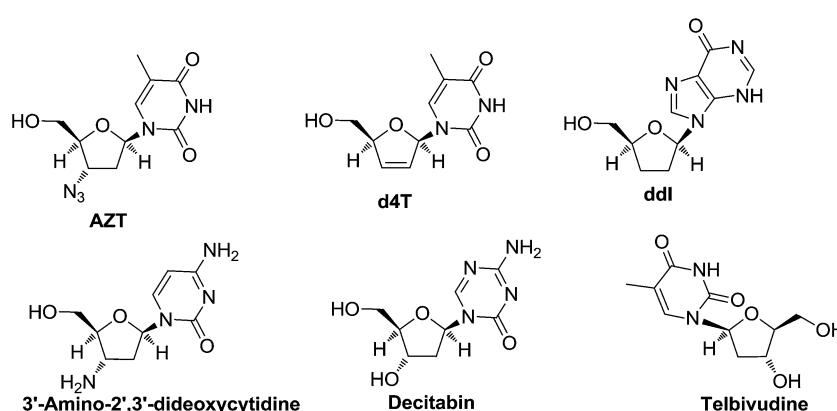
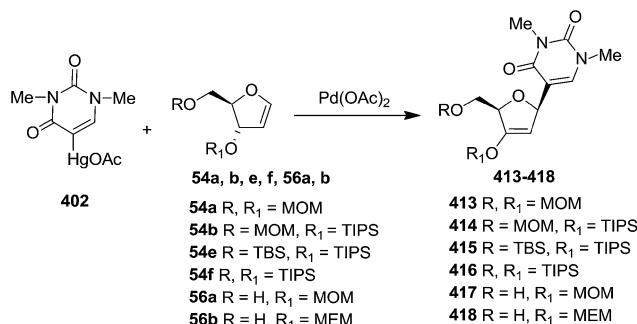


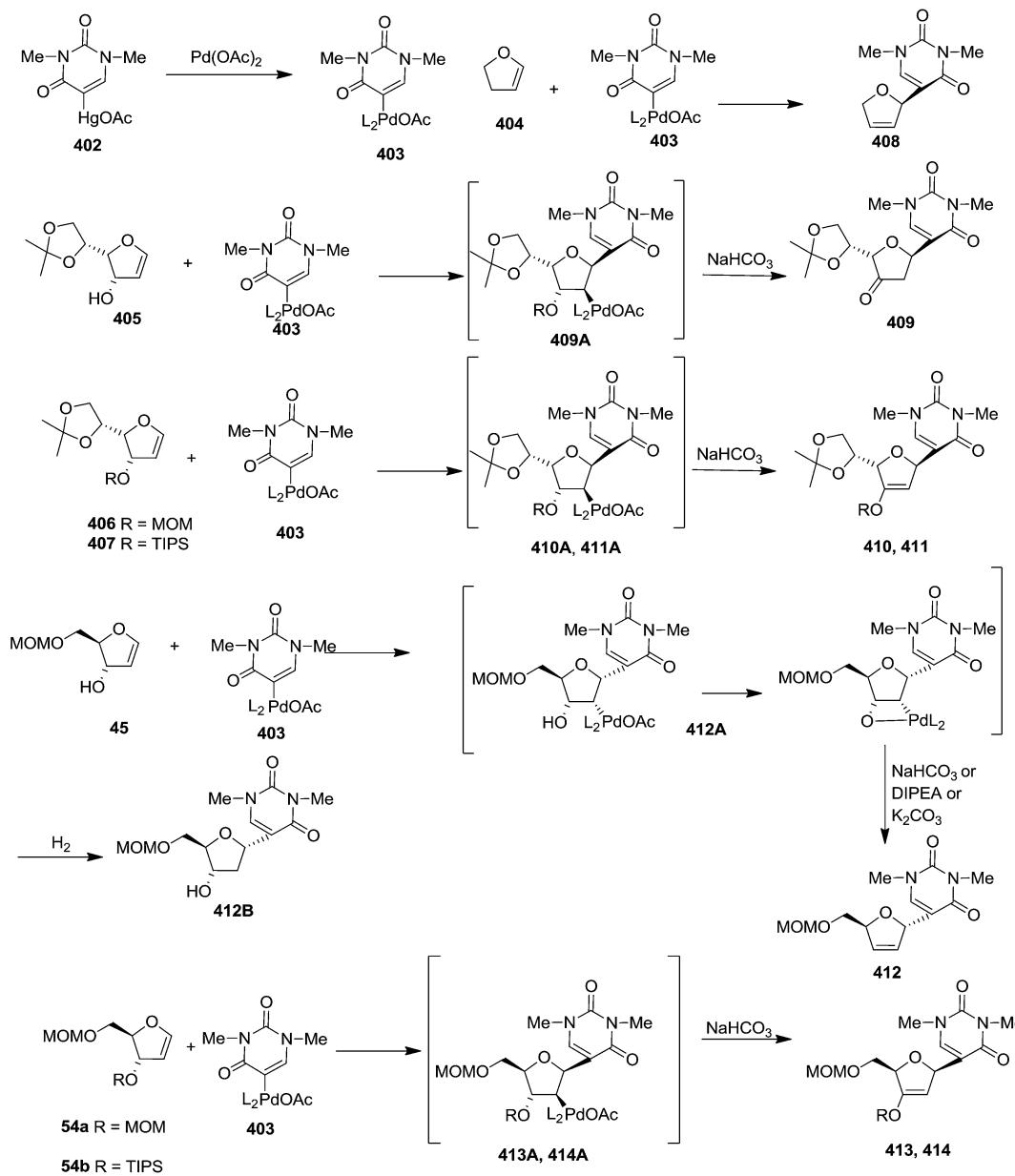
Fig. 4 Structures of some 2'-deoxynucleosides have potent antiviral activity, particularly against human immunodeficiency virus (HIV).



In 1983 Daves Jr and Hacksell showed Heck coupling reactions of furanoid glycanes **404–407**, **45**, **54a**, **54b** with (1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydromimidin-5-yl)mercuric acetate **402** in the presence of a stoichiometric quantity of $\text{Pd}(\text{OAc})_2$ 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 hydro-palladium. 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 glycanes (**45**, **54a**, **54b**) which was depended



Scheme 68



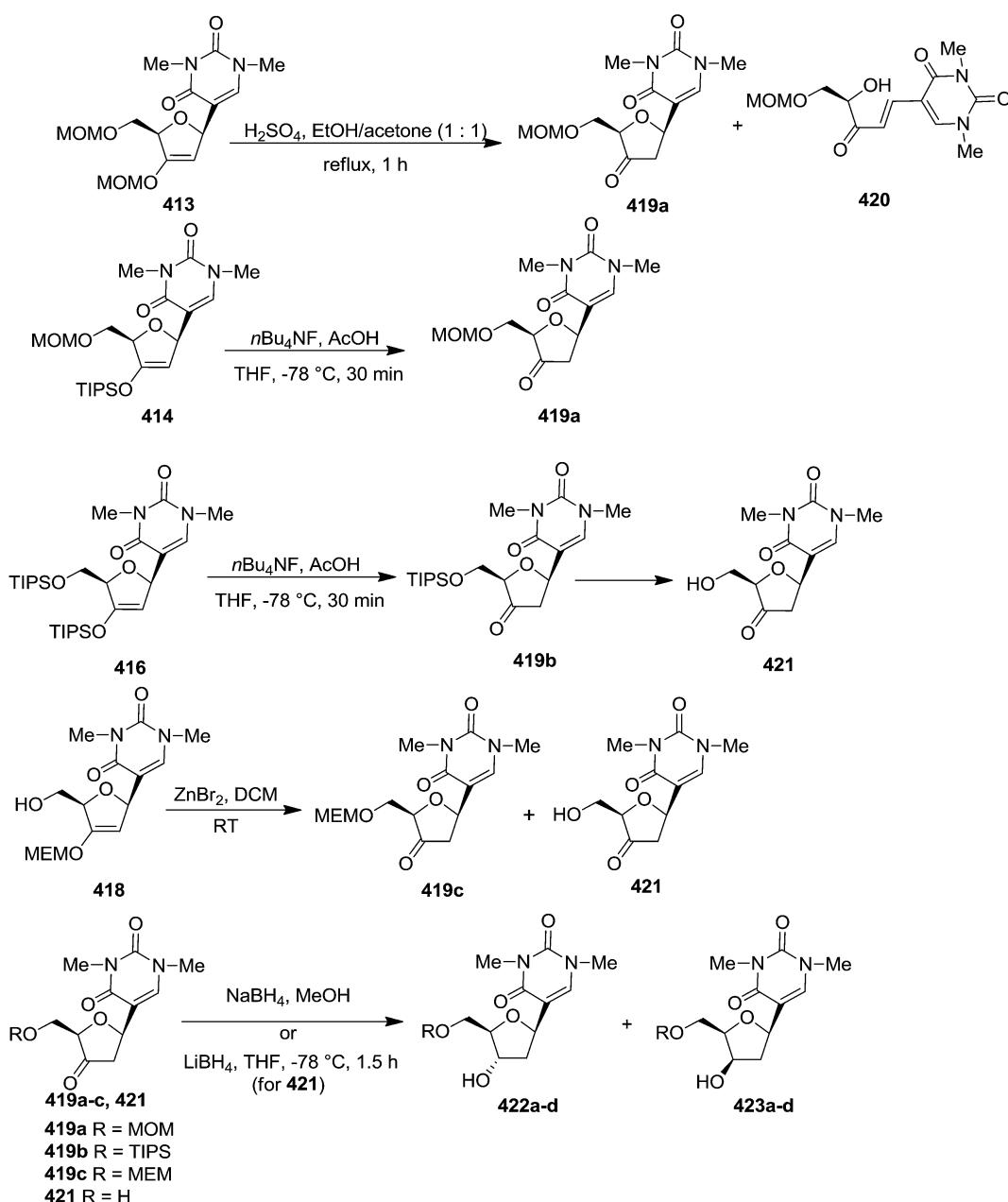
Scheme 67

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 occurred 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 $-78\text{ }^{\circ}\text{C}$ yielded 419a and 419b and/or 421 respectively. The removal of (β -methoxyethoxy)methyl group in 418 by using zinc bromide¹⁴ 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



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

Entry	3'-Keto-C-nucleoside	R	Reducing agents	Temperature °C	Yield ^a %	3'-OH _α /3'-OH _β ^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).

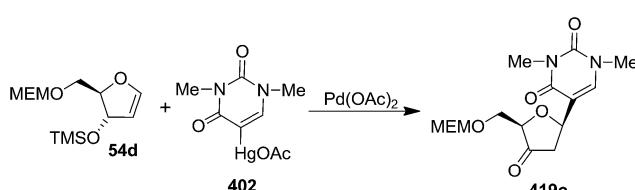
Coupling of 402 with 3,5-O-unsubstituted glycal (1,4-anhydro-2-deoxy-*D*-erythro-pent-1-enitol) 55 produced a mixture of the α - and β -C-nucleosides 421 and 424 in 45% and 29% yields, respectively. Coupling of 402 with 5-O-substituted glycal 53c gave α -C-nucleoside 424 as the sole product *via* formation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

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

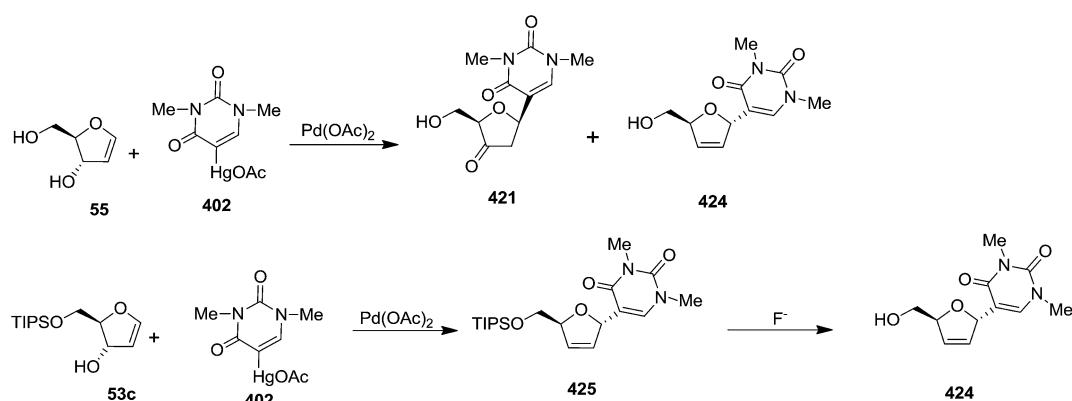
brominated at *para* position to -OMe with NBS in DMF at room temperature for 30 min to give 427 in 81% yield, which on treatment with hexa-*n*-butylditin (*n*Bu₃Sn)₂ in the presence of 2.0 mol% of Pd(PPh₃)₄ in toluene (N₂, 115 °C, 12 h) produced stannane 428 in 65% yield. Its coupling with furanoid glycal 54b in the presence of stoichiometric Pd(OAc)₂ in CH₃CN 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 *n*Bu₄NF 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 NaBH₄, H₂O 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 *n*Bu₃N, 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

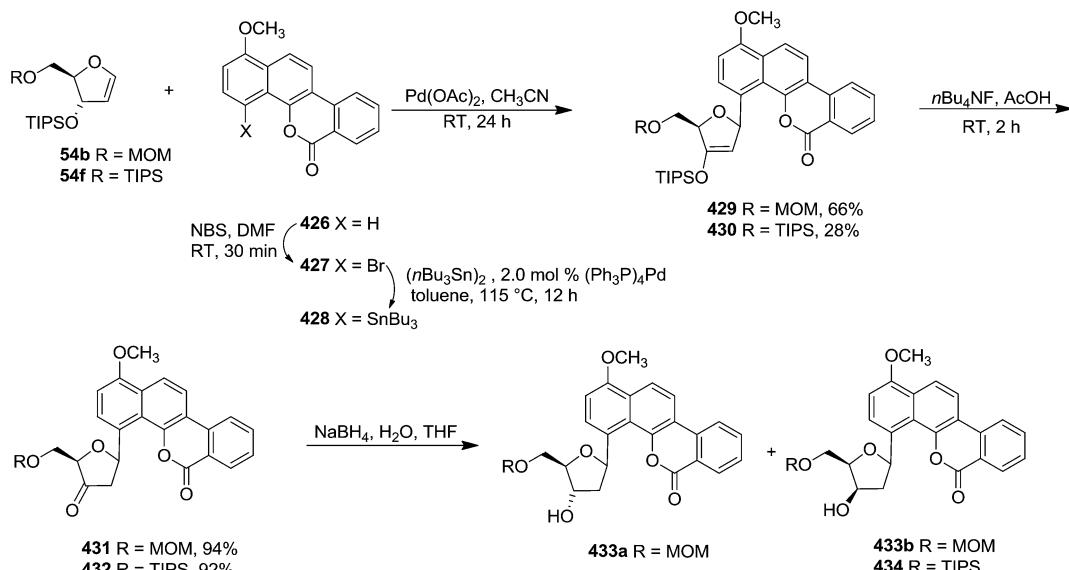


Scheme 70

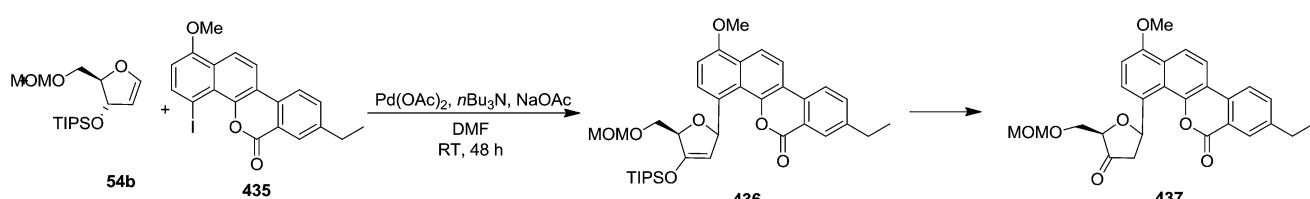


Scheme 71

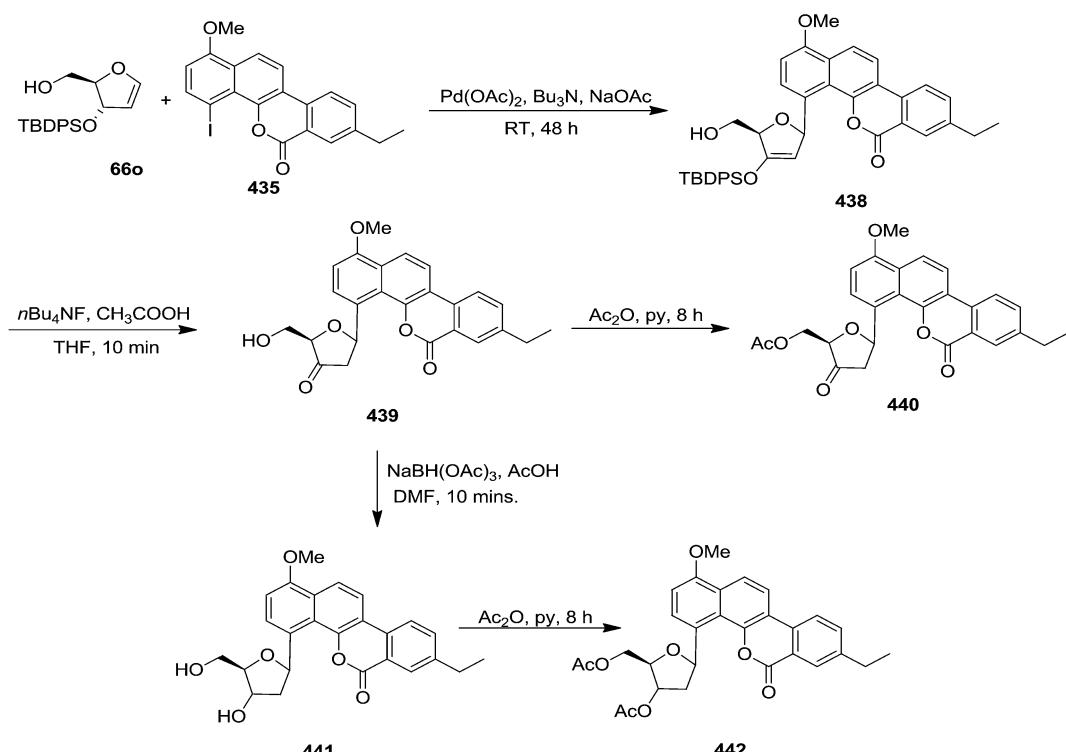




Scheme 72

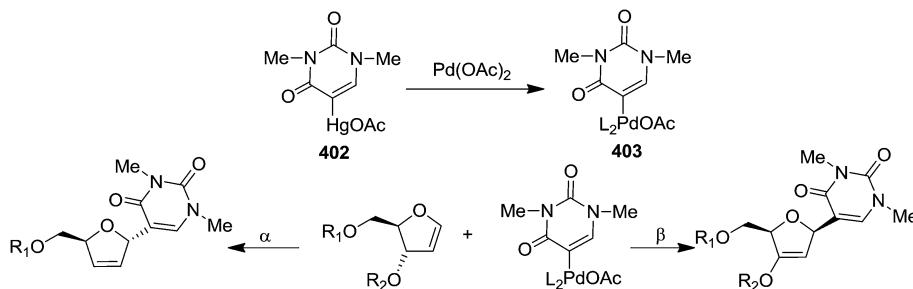


Scheme 73



Scheme 74





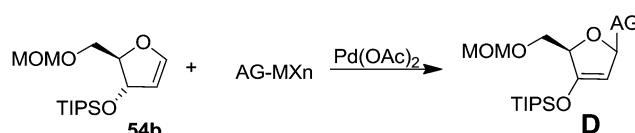
Scheme 75

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 *n*Bu₄NF 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	Substituents of (A)	% yield of α - <i>C</i> -nucleosides (B)	% yield of β - <i>C</i> -nucleosides (C)
1	55 R ₁ = R ₂ = H	29 (443a)	45 (443b)
2	56a R ₁ = H, R ₂ = MOM	0	65 (417)
3	45 R ₁ = MOM, R ₂ = H	78 (412)	0
4	54a R ₁ = R ₂ = MOM	0	71 (413)
5	54b R ₁ = MOM, R ₂ = TIPS	0	92 (414)
6	54f R ₁ = R ₂ = TIPS	0	51 (416)
7	66o R ₁ = H, R ₂ = TBDPS	0	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	<i>C</i> -Glycoside product, % yield (D)
1	445	96
2	446	57
3	447	70
4	448	57
5	428	66

In this report, Daves Jr also showed the comparative study of coupling reaction of aglycon-mercuric acetate and tri-*n*-butyl-stannyl 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 **660** and pivaloyl protected aglycon derivative **449**.⁶⁵

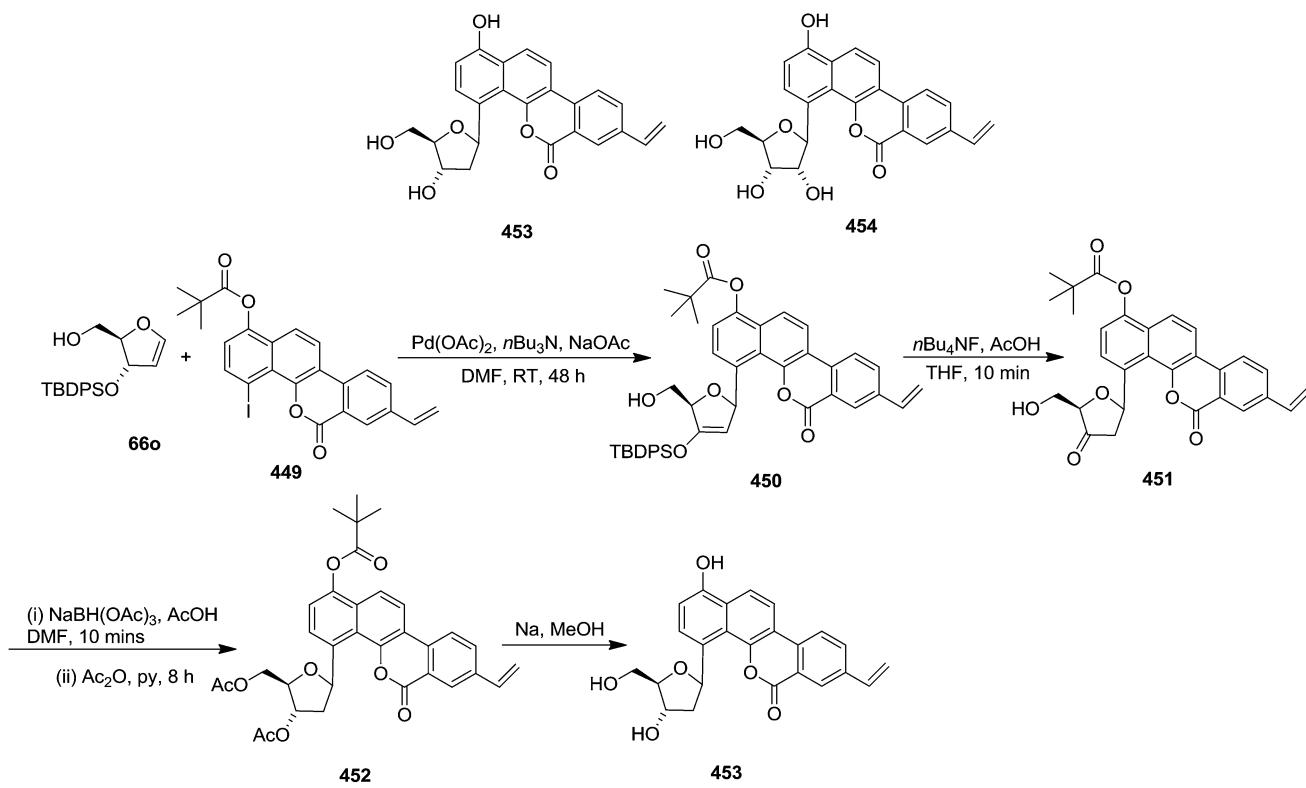
They further extended their study and showed the utility of regio- and stereospecific *C*-glycosyl bonds formation by the synthesis of *C*-nucleoside analogs. They synthesized 2'-deoxy-pseudouridin **458** in three steps by utilizing the palladium-mediated coupling of 5-iodouracil **455** with glycal **660**, 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 $\text{NaBH}(\text{OAc})_3$ 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

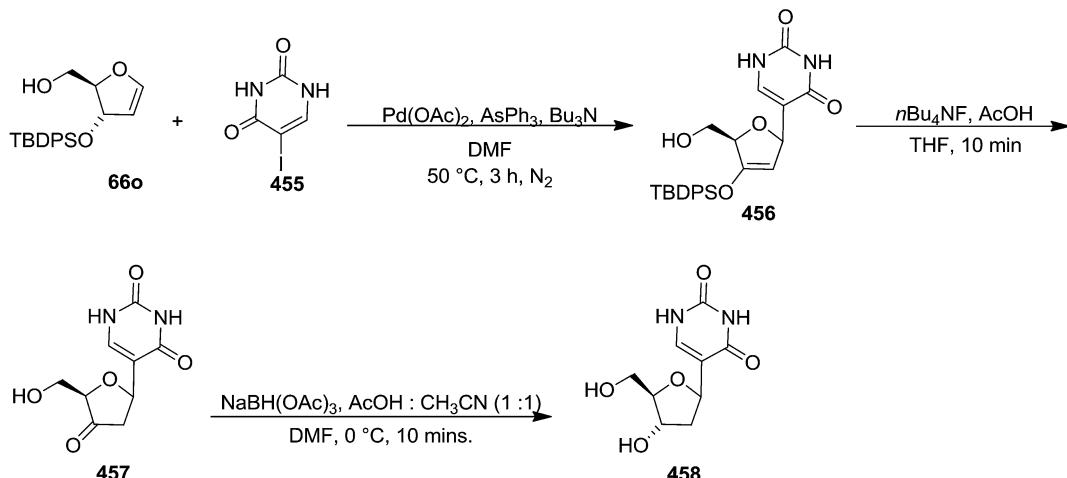
660 and bis(tetrahydropyranyl) protected iodo aglycon derivative **459** underwent regio and stereospecific coupling reaction in the presence of $\text{Pd}(\text{dba})_2$ as catalyst and triphenylarsine as ligand in acetonitrile to give *C*-nucleoside **460** in 62% isolated yield. Following the similar 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 *n*Bu₃SnH/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

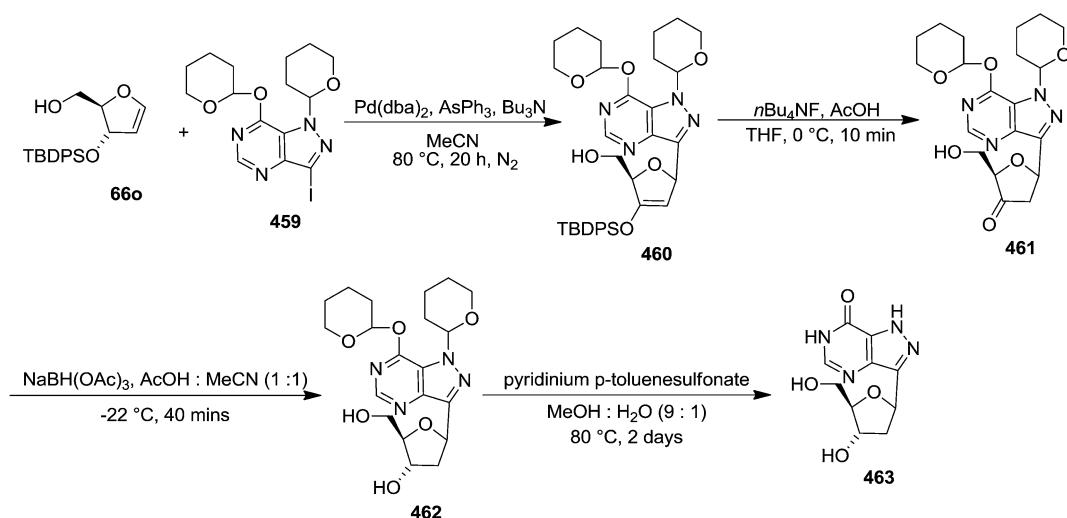
Daves Jr have reported the synthesis of 1-(tri-*n*-butylstannyl)furanoid glycals for the first time by lithiation of the corresponding 3-*O*-unsubstituted glycals (404, 469, 55, 53b) followed by reaction with *n*Bu₃SnCl. They also discussed the tri-*n*-butylstannylation of 3-*O*-substituted hydroxy glycal 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



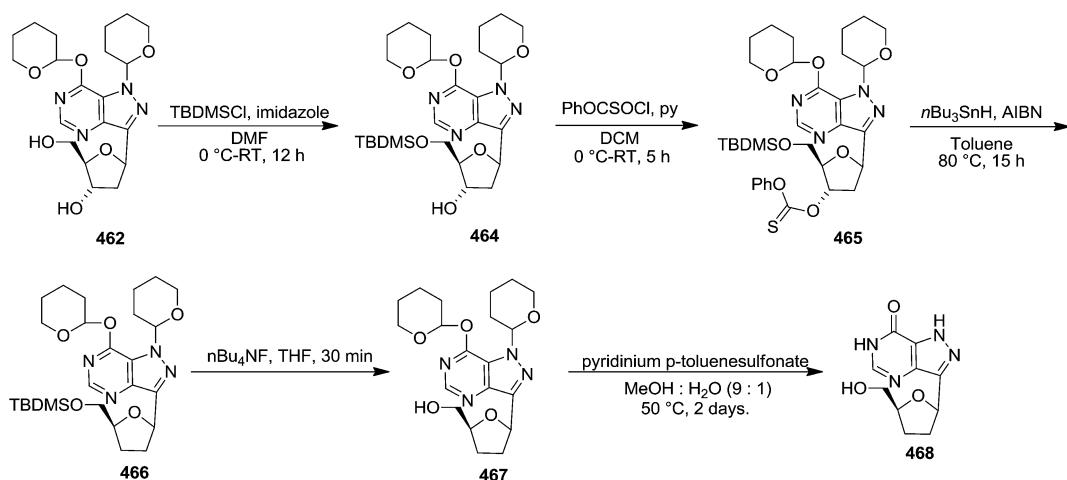
Scheme 77



Scheme 78



Scheme 79



Scheme 80



treated with $n\text{Bu}_3\text{SnH}$ 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 $\text{NaBH}(\text{OAc})_3$ yielded the 2'-deoxyribofuranosyl *C*-nucleoside **487** in 65% yield for the three steps (Scheme 82).

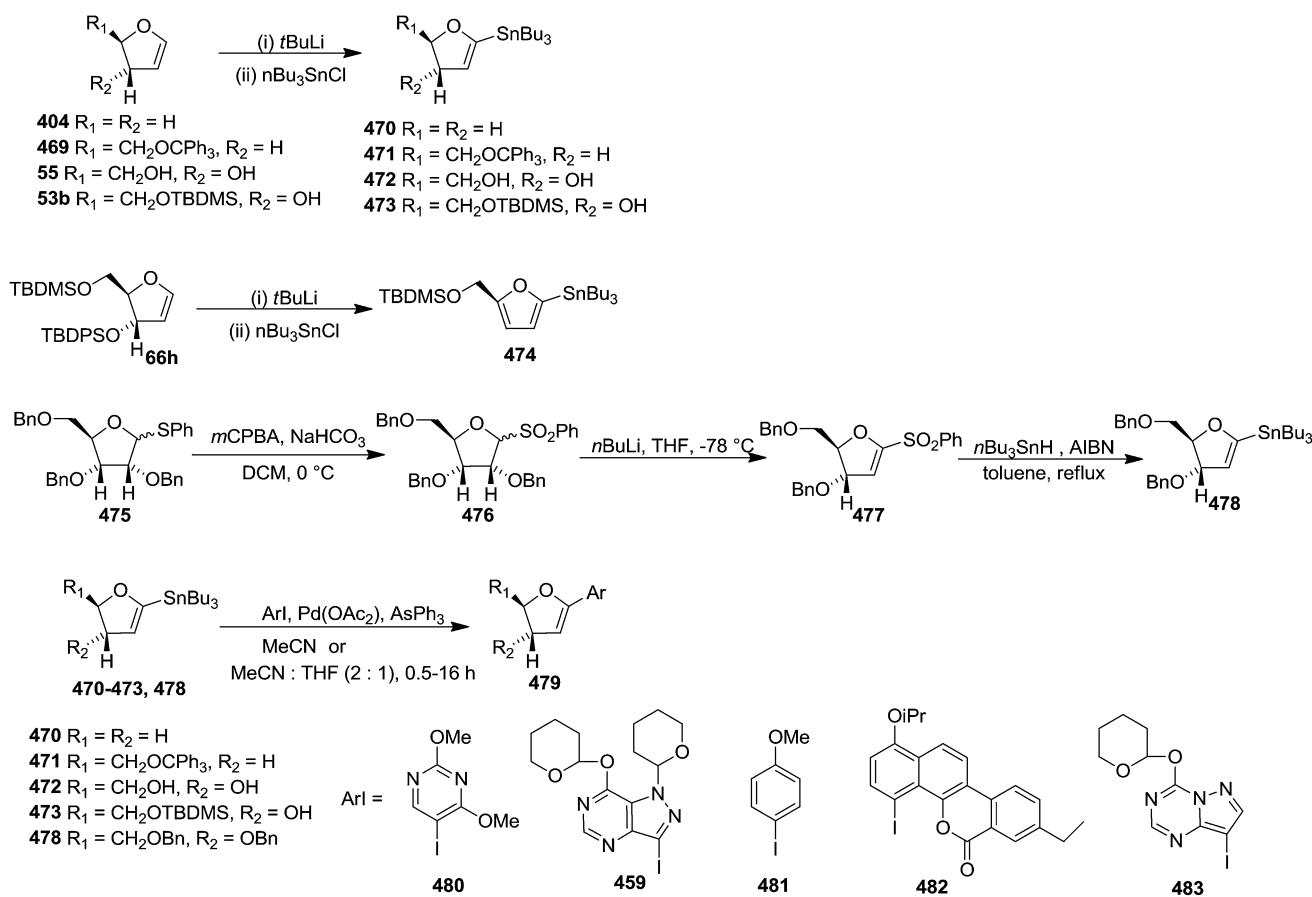
Similarly, they synthesized palladium-mediated coupling of 8-iodo-4-methoxypyrazolo[1,5-*a*]-1,3,5-triazine **488** and furanoid glycal **66o** efficiently produced *C*-nucleoside intermediate **489** which was desilylated to form 3'-keto *C*-nucleoside **490** (Scheme 83).

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 $\text{Pd}(\text{dba})_2$ and 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 $\text{NaBH}(\text{OAc})_3$. 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*-

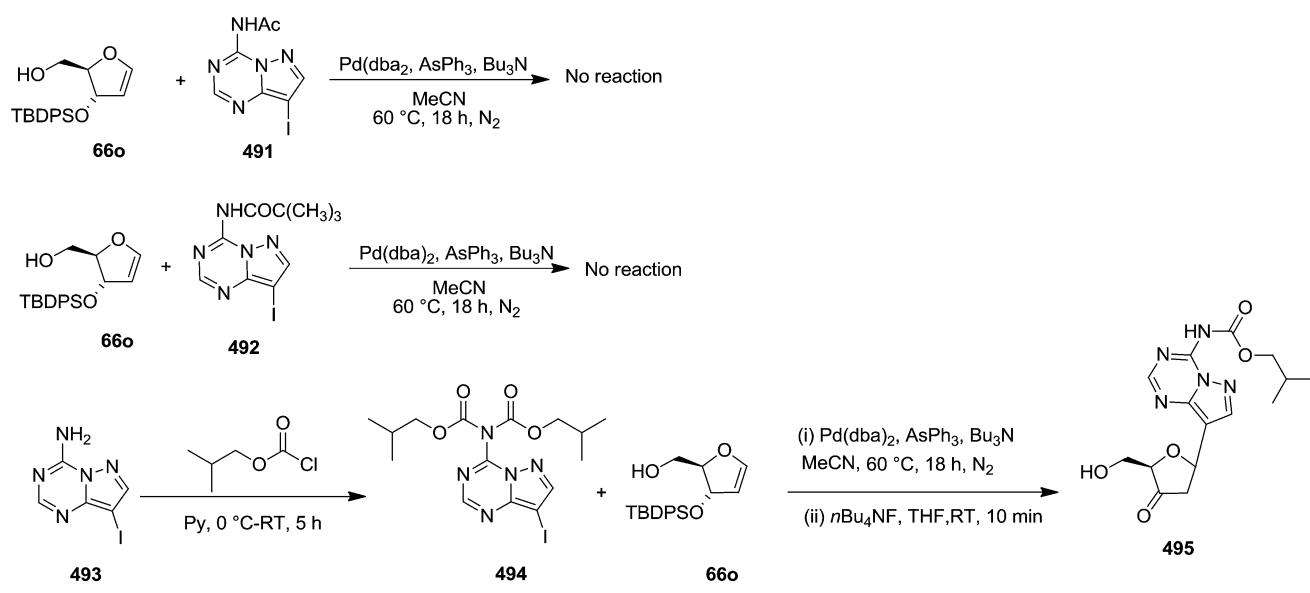
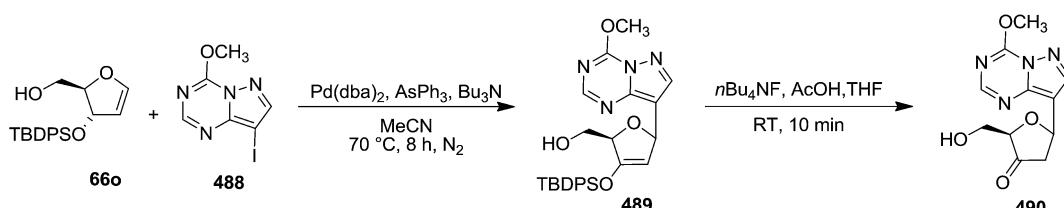
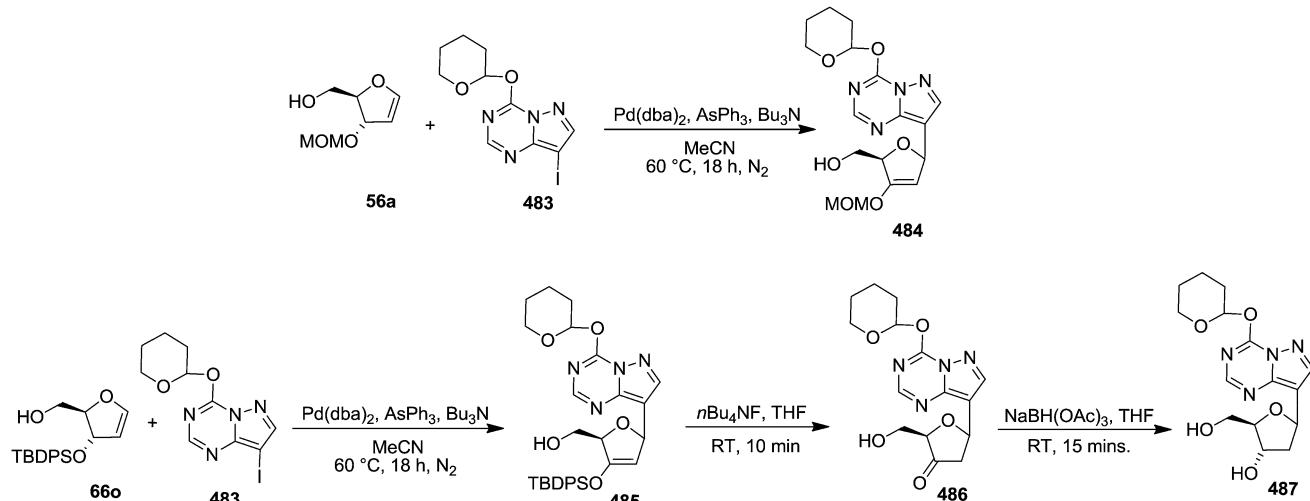


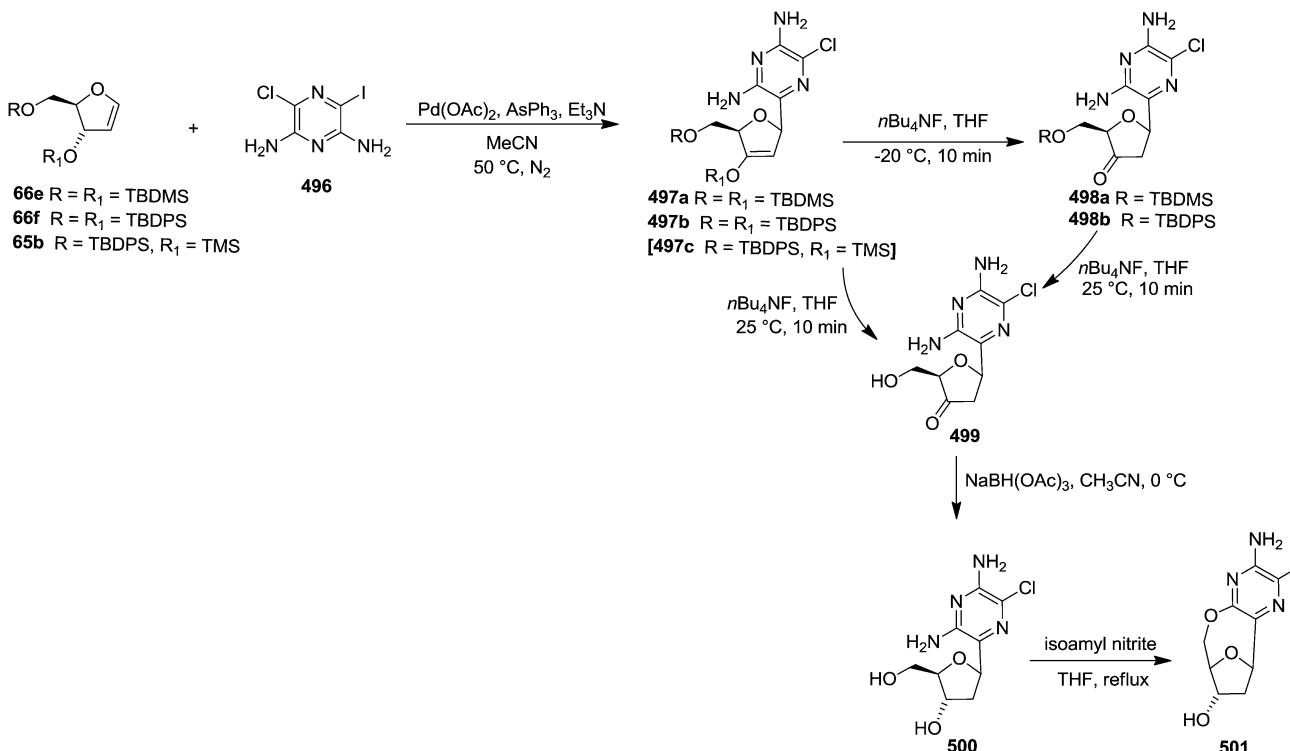
Scheme 81



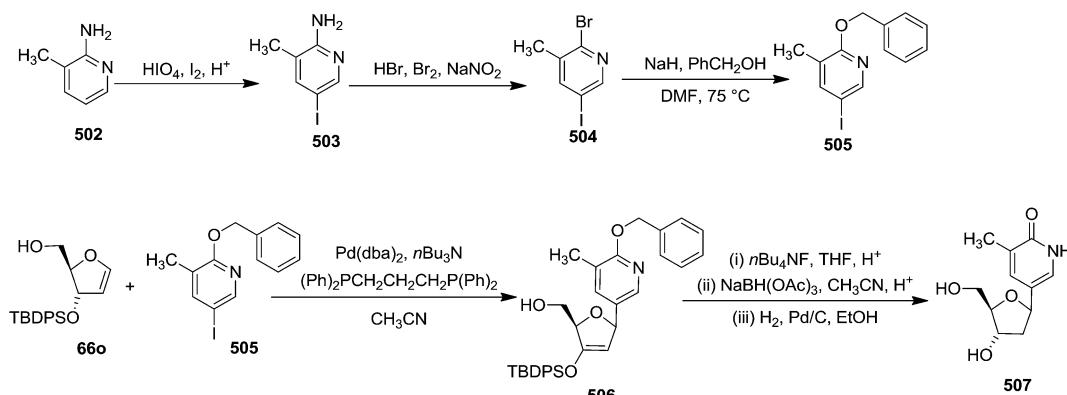
nucleosides **507** and **512**, “deletion modified” analogues of dT and dC.⁷⁰ After several trial and error, they prepared 2-(benzyloxy)-3-methyl-5-iodopyridine **505** from **502** in three steps. Pd-mediated coupling reaction of glycal **66o** and 2-(benzyloxy)-3-methyl-5-iodopyridine **505** in the 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 85



Scheme 86

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

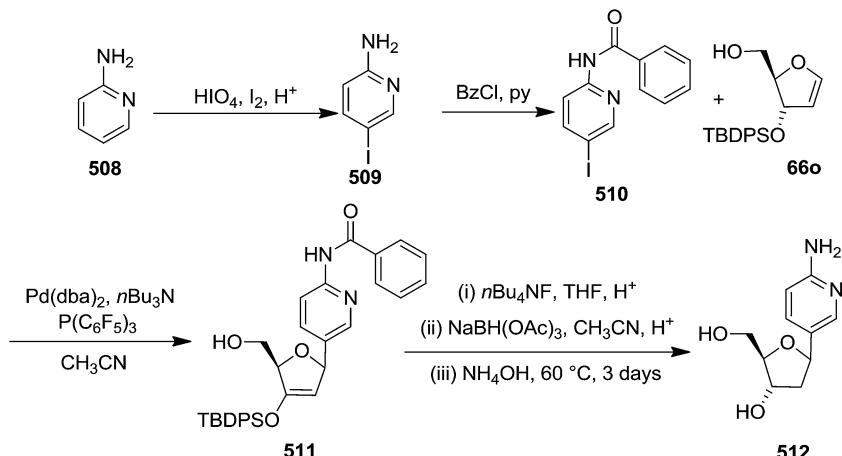
In a similar fashion, they prepared the *C*-nucleoside analogue of dC 512 from 2-aminopyridine 508. They prepared 510 from 508 by its iodination followed by amino group protection with BzCl of the resulting iodo derivative 509. The coupling reaction of glycal 66o with 510 in the presence of Pd and an ancillary ligand P(C₆F₅)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 66n²³ in the usual procedure.⁷¹

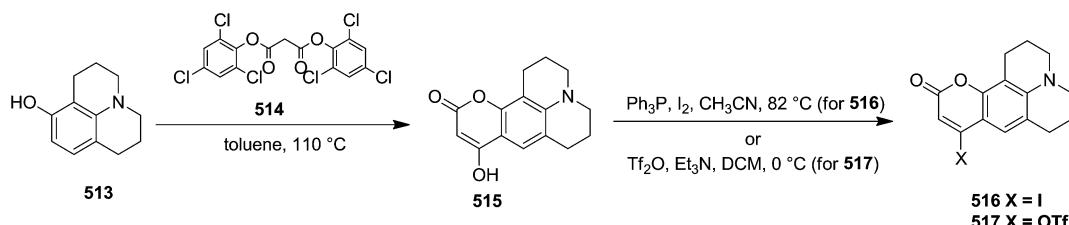
Coumarin 515 (X = OH) was prepared from 8-hydroxyjulolidine 513. Reaction of 513 with bis(2,4,6-trichlorophenyl) malonate 514 in refluxing toluene effected annulation of the α -pyrone ring system to afford 515 in excellent yields (94%). Its hydroxyl functionality could be transformed to the iodide by treating it with a preformed complex of triphenylphosphine and iodine (Ph₃P, I₂, CH₃CN, 82 °C) to form 516. Alternatively, the hydroxyl group could be acylated with trifluoromethanesulfonic anhydride (Tf₂O, Et₃N, 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).

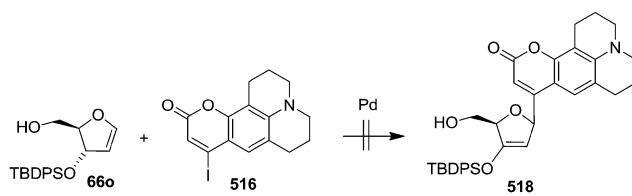




Scheme 87



Scheme 88



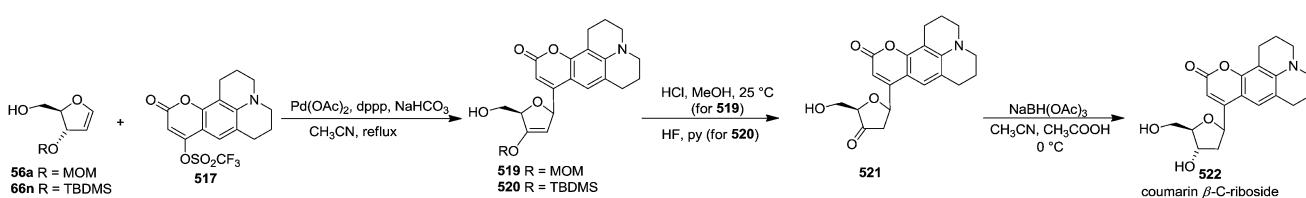
Scheme 89

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. NaHCO₃ in CH₃CN under refluxing condition to obtain Heck product **519** (75% yield) and **520** (79% yield) respectively. Hydrolysis of **519** under acidic conditions (HCl, CH₃OH, 25 °C) afforded ketone **521**. Fluoride-promoted cleavage (HF/pyridine) of the silyl ether **520** afforded ketone **521** in excellent yields. The

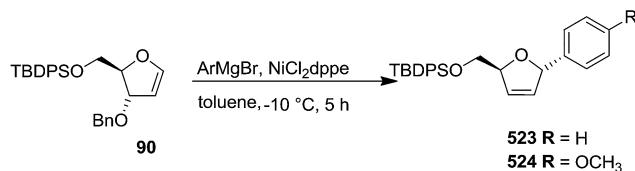
carbonyl group of **521** was reduced stereoselectively to the *ribo*-glycoside **522** with NaBH(OAc)₃ (Scheme 90).

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, Ph₃As, and Et₃N in dry CH₃CN 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

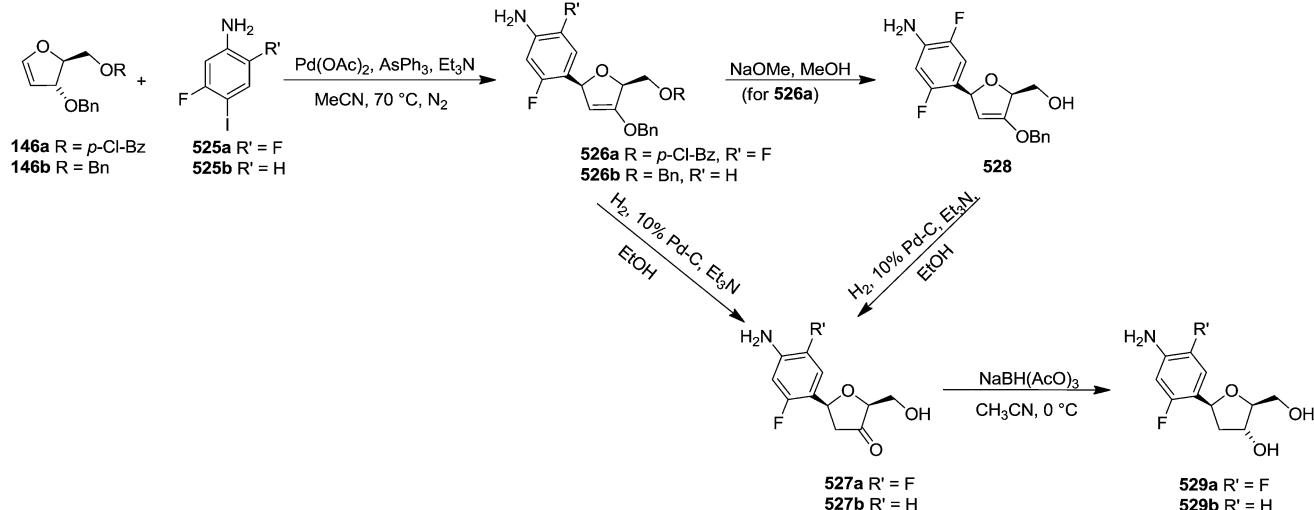


Scheme 90

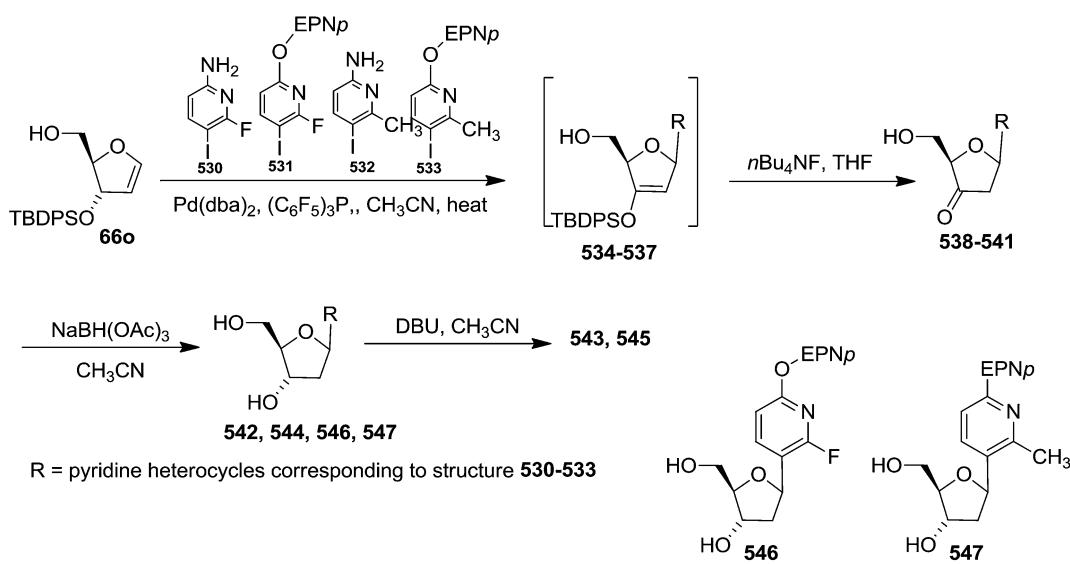
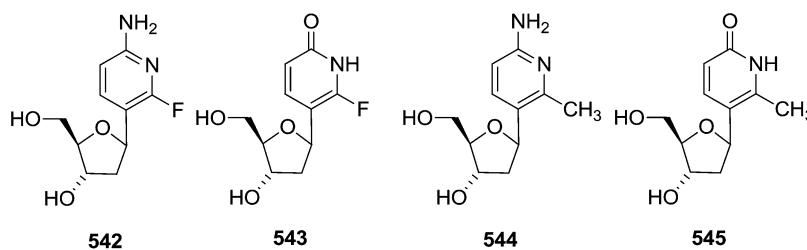


Scheme 91

EtOH containing several drops of Et₃N 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 Et₃N at 60 °C. Subsequent reduction of the hydroxy ketones (527a, b) with NaBH(AcO)₃ in dry



Scheme 92



Scheme 93



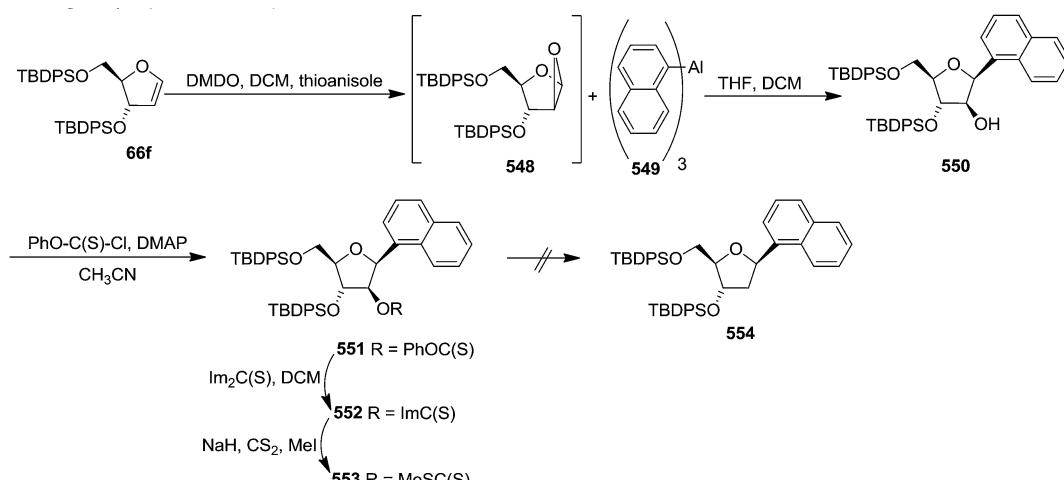
CH_3CN afforded the target deoxy- β -L-cytidine *C*-nucleoside mimics (**529a, b**) (Scheme 92).

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 $\text{Pd}(\text{dba})_2$ and $(\text{C}_6\text{F}_5)_3\text{P}$ in acetonitrile to give β -*C*-nucleoside intermediates (**534–537**), which, without isolation, were desilylated with $n\text{Bu}_4\text{NF}$ 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).

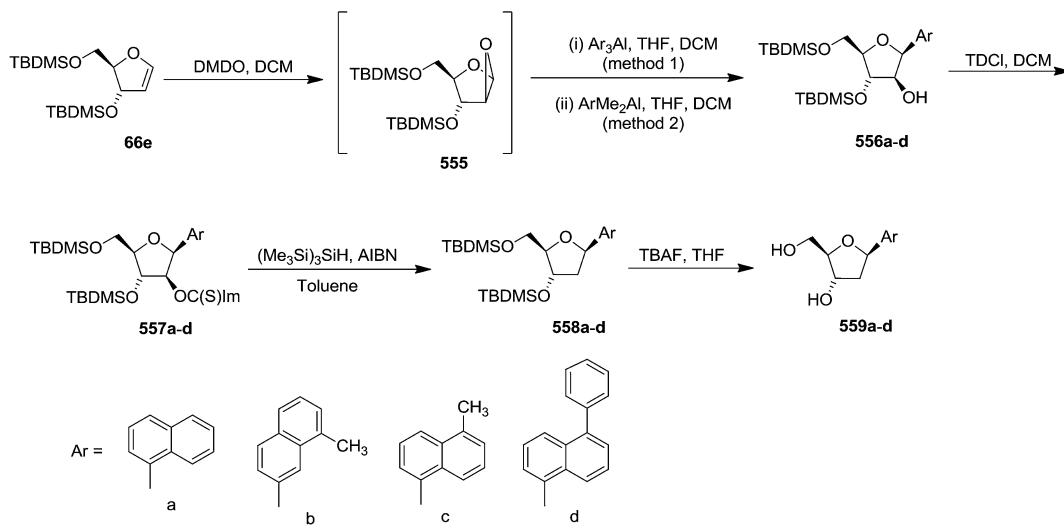
Seitz and Singh diastereoselectively synthesized β -aryl-*C*-2-deoxynucleosides from furanoid glycal derived glycal epoxides.⁷⁴ The glycal **66f** on treatment with DMDO in DCM at 0 °C

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 $n\text{Bu}_3\text{SnH}$ or $(\text{TMS})_3\text{SiH}$ in presence of AIBN due to the bulkiness of the two TBDS groups (Scheme 94).

Then they selected TBDS-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 thiocarbonylimidimidazole to form **557a**, which on reduction with $(\text{TMS})_3\text{SiH}$ and AIBN furnished 2'-deoxynucleoside **558a** in 82% yield. Finally, the silyl ether deprotection was performed by treatment with $n\text{Bu}_4\text{NF}$ in THF to afford fully deprotected 2'-deoxy-1'- β -naphthyl nucleoside

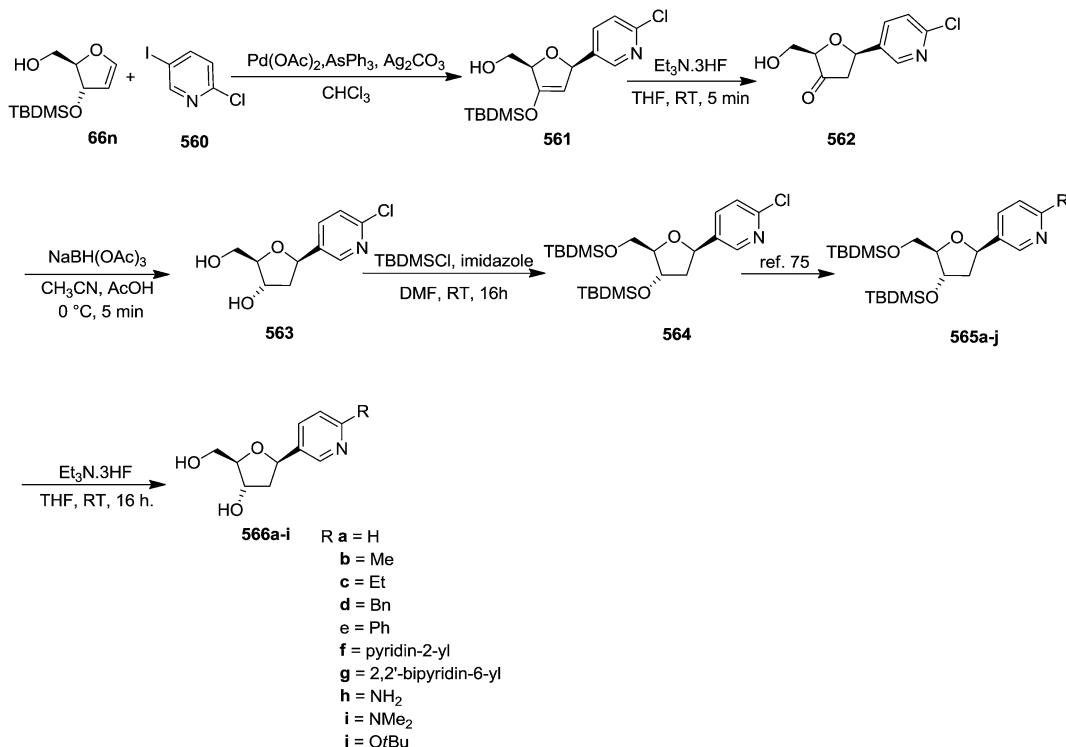


Scheme 94

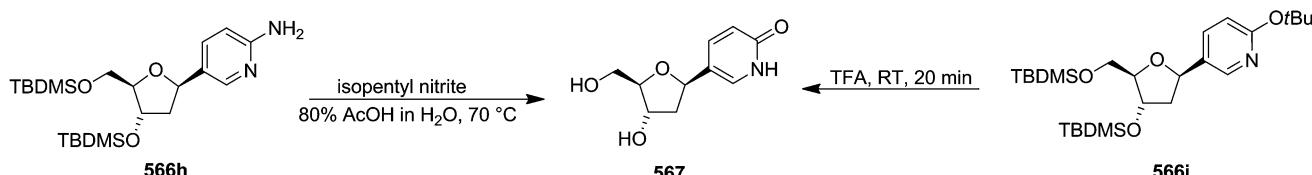


Scheme 95





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/AsPh₃ and Ag₂CO₃ 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 H₂ over Pd/C for 3 h, in a mixture of EtOH, THF, and H₂O, in presence of Et₃N. 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 1 β -(6-amino-, and 6-*tert*-butoxypyridin-3-yl)-2'-deoxyribonucleosides 565h-j in good yields. All the silylated nucleosides 565a-i were deprotected using Et₃N·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

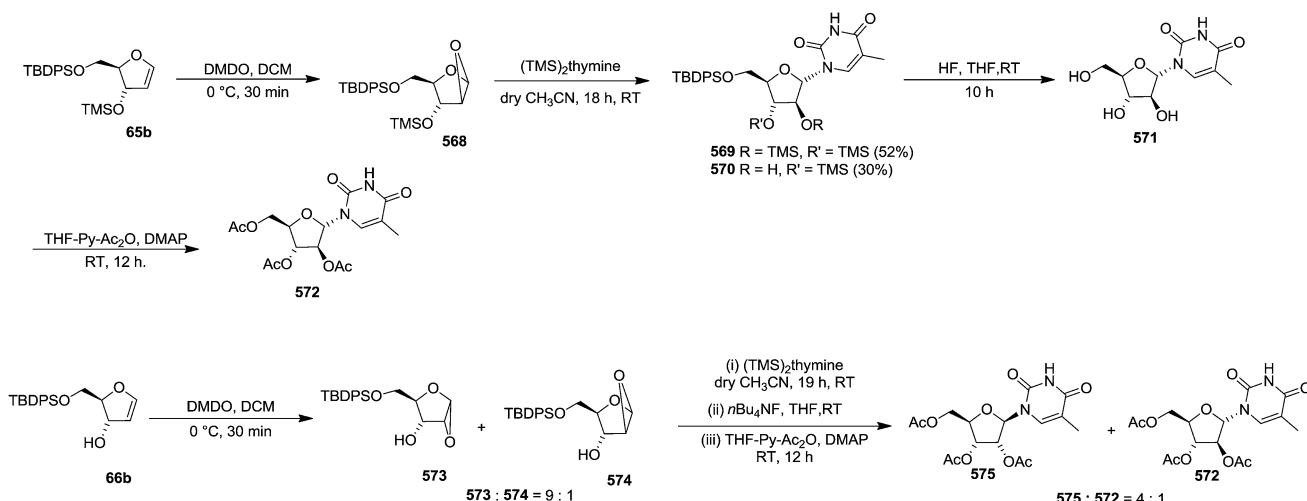


synthesis of nucleosides.⁸ The epoxidation of furanoid glycal **65b** with DMDO (dimethyldioxirane) was highly face selective to give **568**. The treatment of the epoxide **568** with (TMS)₂thymine provided a mixture of **569** (52% yield) and **570** (30% yield). The mixture was deprotected with TBAF in THF to afford **571**. Its acetylation with Ac₂O-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)₂thymine 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).

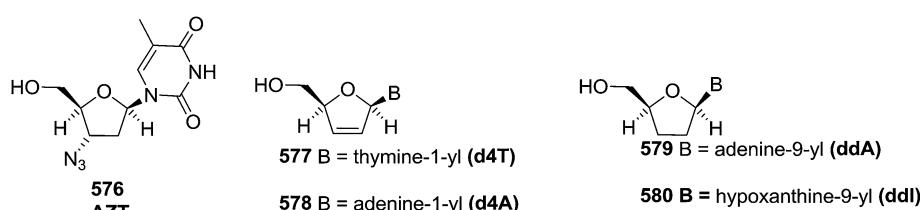
In 1991 Kim *et al.* prepared phosphonate isosteres of **577** (d4T), **578** (d4A), and **579** (ddA) (Fig. 5) monophosphates using regiospecific and highly stereoselective electrophilic addition to furanoid glycals as the key step.⁷⁶ The starting material for this study was the glycal **582**, which 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 $-70\text{ }^{\circ}\text{C}$, 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

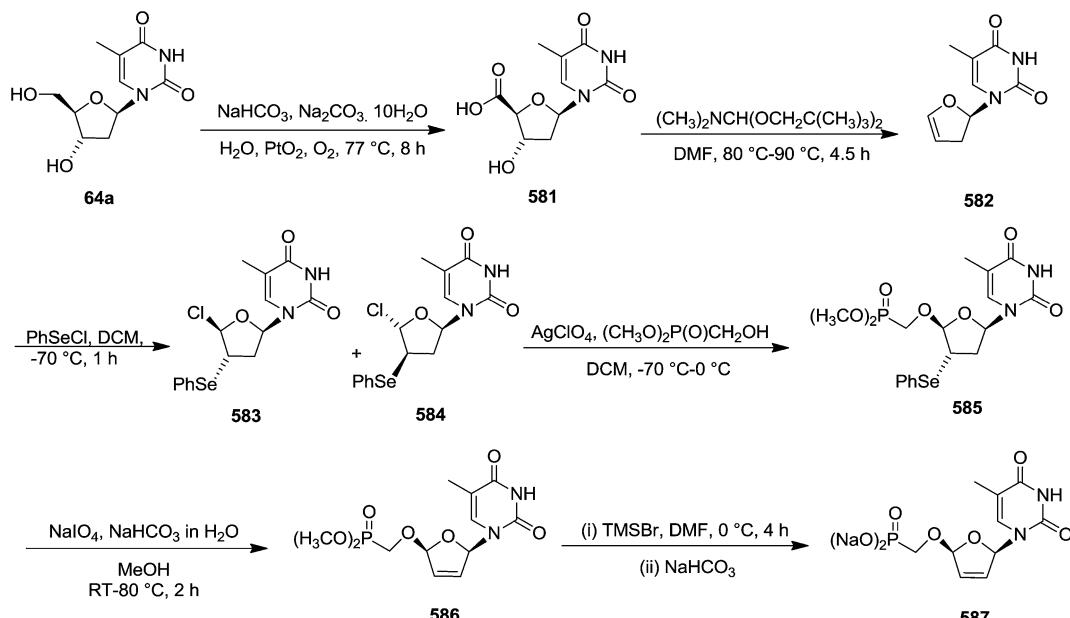
41% overall yield. It was then transformed into the d4T phosphonate analogue **587** by the sequential oxidation with sodium periodate in methanol followed by phosphonate ester removal of the resulting **586** with TMSBr in DMF and finally by neutralization with NaHCO₃ in overall 52% yield (Scheme 99). 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 tetrahydrofuran 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 OsO₄ 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).

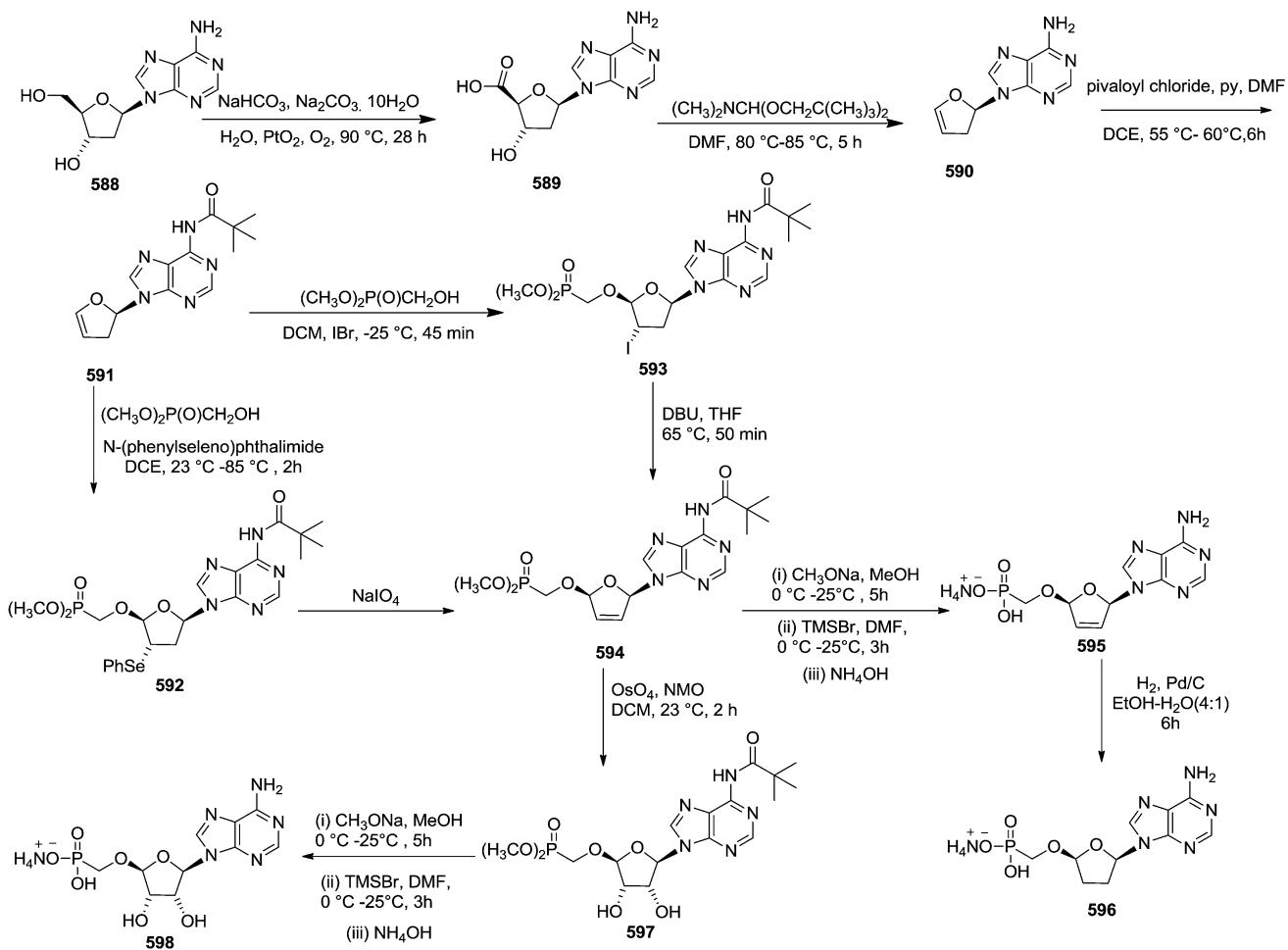


Scheme 98

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



Scheme 99



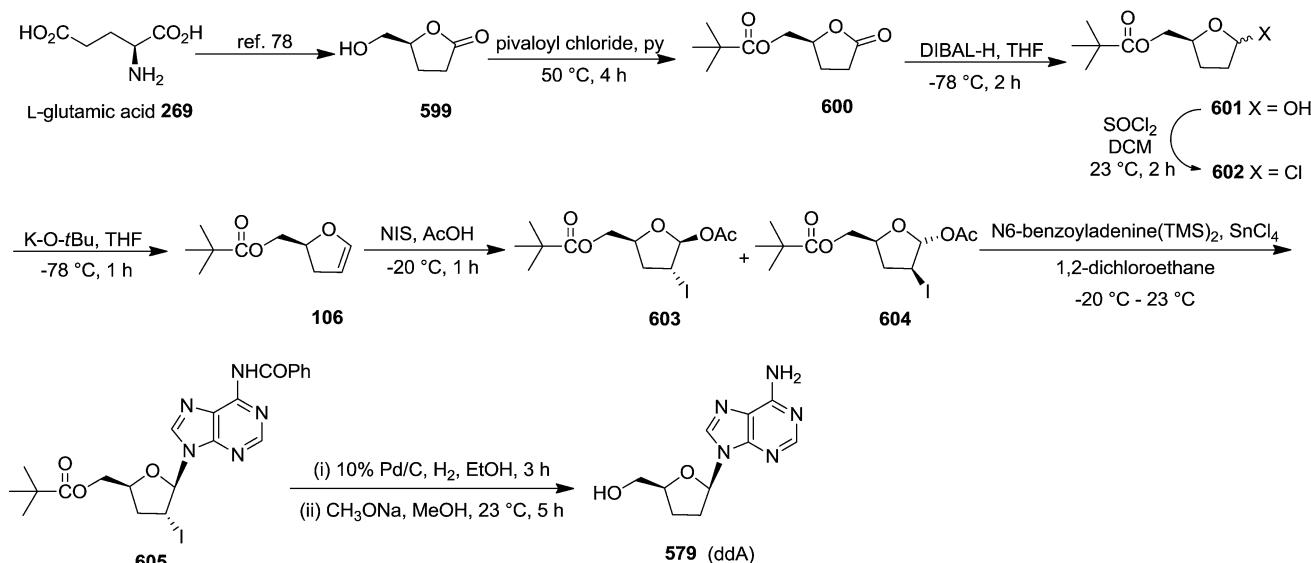
Scheme 100



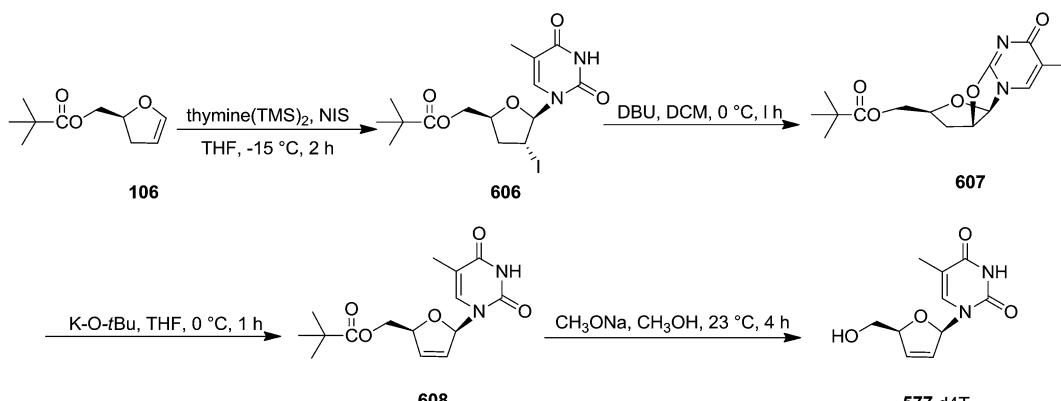
In 1992, Kim and Misco, demonstrated highly stereoselective synthesis of d4T 577 and ddA 579, antiviral nucleosides, from L-glutamic acid 269 *via* furanoid glycal intermediate.⁹ The synthesis of the requisite furanoid glycal 106 was derived from the known lactone 599 which was in turn, readily available by the diazotization-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 $\text{KO}t\text{Bu}$ 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 $\text{KO}t\text{Bu}$ in THF produced olefin 608 (82% yield) which on acyl deprotection with NaOMe yielded 577 (d4T) in 95% yield.

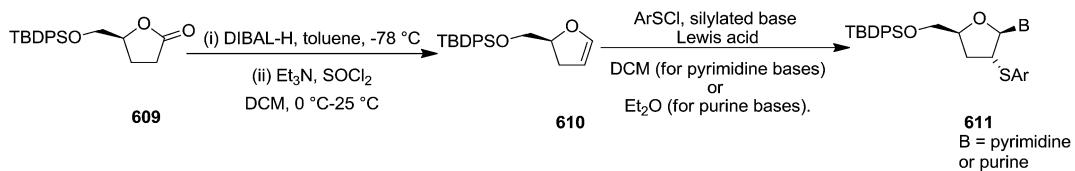
Liotta *et al.* described the synthesis of nucleosides *via* region- and stereoselective electrophilic addition to furanoid glycals 610 which was prepared from lactone 609 in a straightforward fashion.⁷⁹ The DIBAL-H reduction of 609 followed by addition of SOCl_2 and Et_3N to the corresponding lactol 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

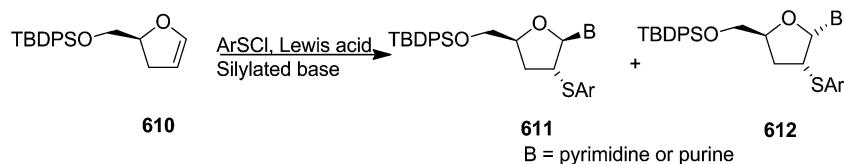


Scheme 102



Scheme 103

Table 11 Additions of arylsulphenyl chlorides/silylated bases to glycals



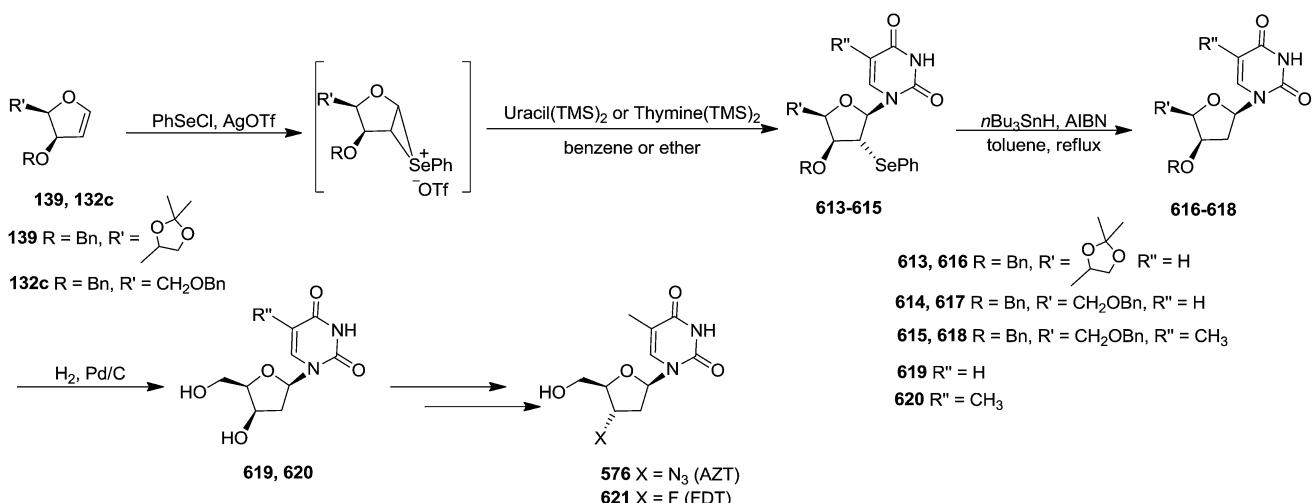
Entry	ArSCl	Lewis acid ^a	Silylated base	Conditions ^b (°C)	Ratio ($\beta : \alpha$)	Time (h)	Yield (%)
1	PhSCl	SnCl ₄	<i>N</i> -Ac-Cytosine	-78 to 25	18 : 1	2	65
2	PhSCl	TMSOTf	<i>N</i> -Ac-Cytosine	-78 to 0 to 25	5 : 1	1.5	60
3	TIPPSCl	SnCl ₄	<i>N</i> -Ac-Cytosine	-78 to 25	23 : 1	2	70
4	TIPPSCl	TMSOTf	<i>N</i> -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 sulphenyl 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 sulphenyl 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).

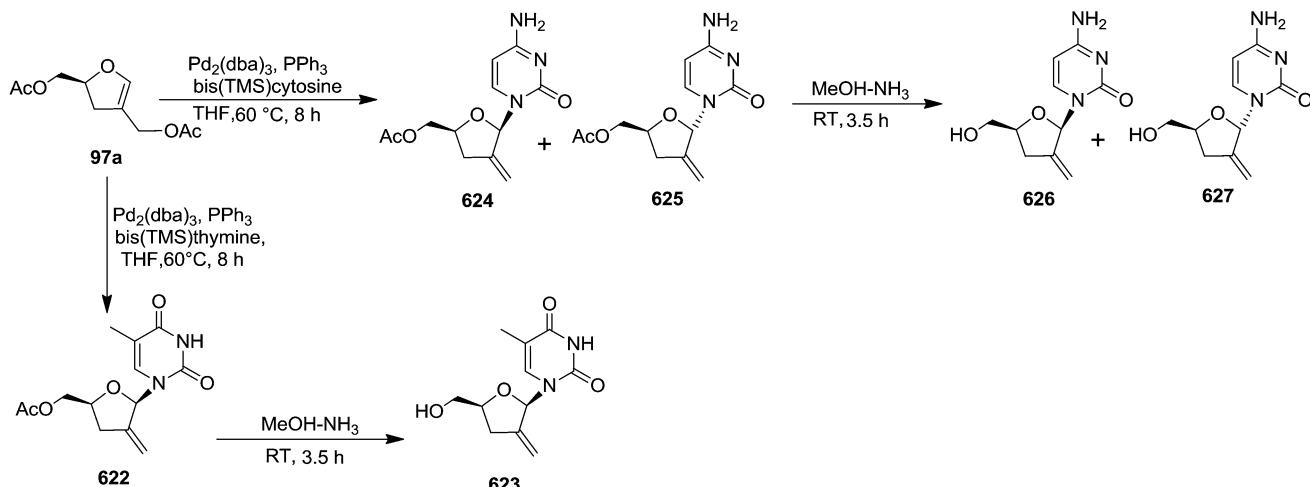
In 1993, Castillón and co workers showed selenium controlled stereoselective synthesis of a series of 2'-deoxy

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*-

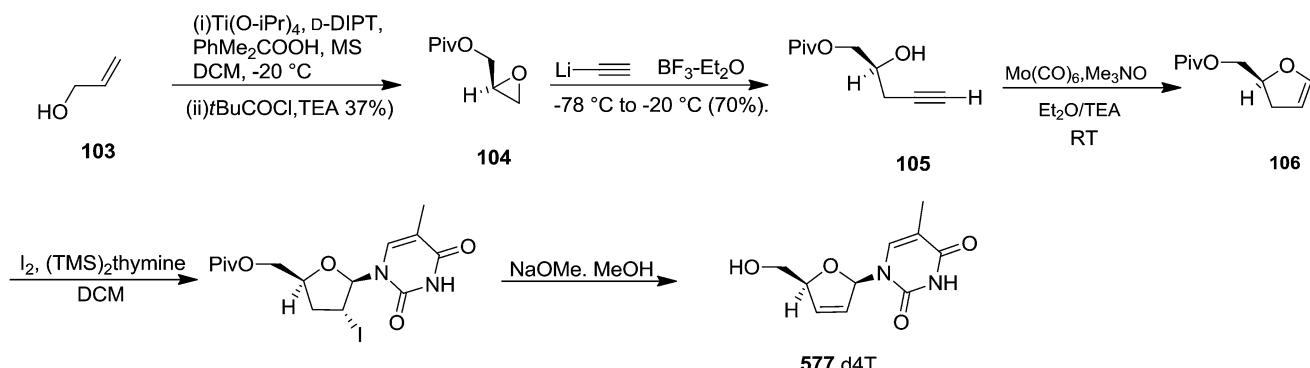


Scheme 104





Scheme 105

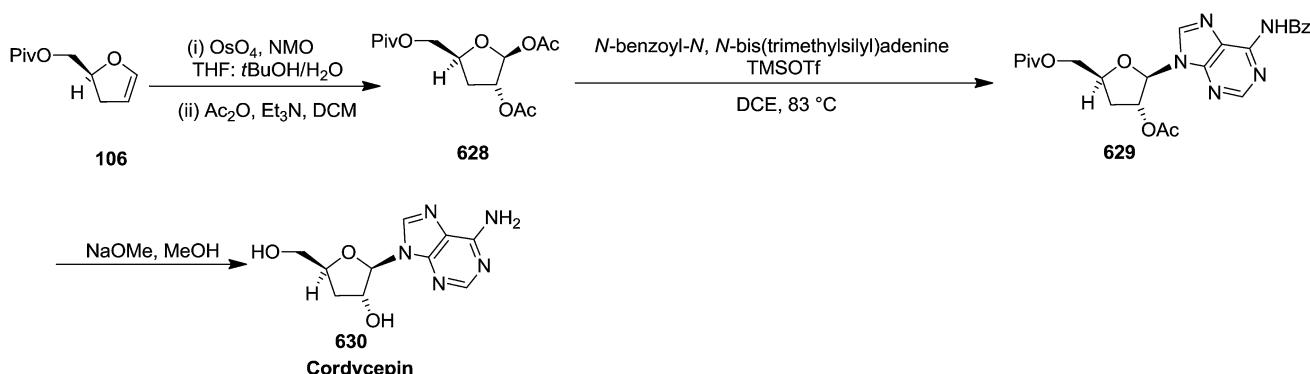


Scheme 106

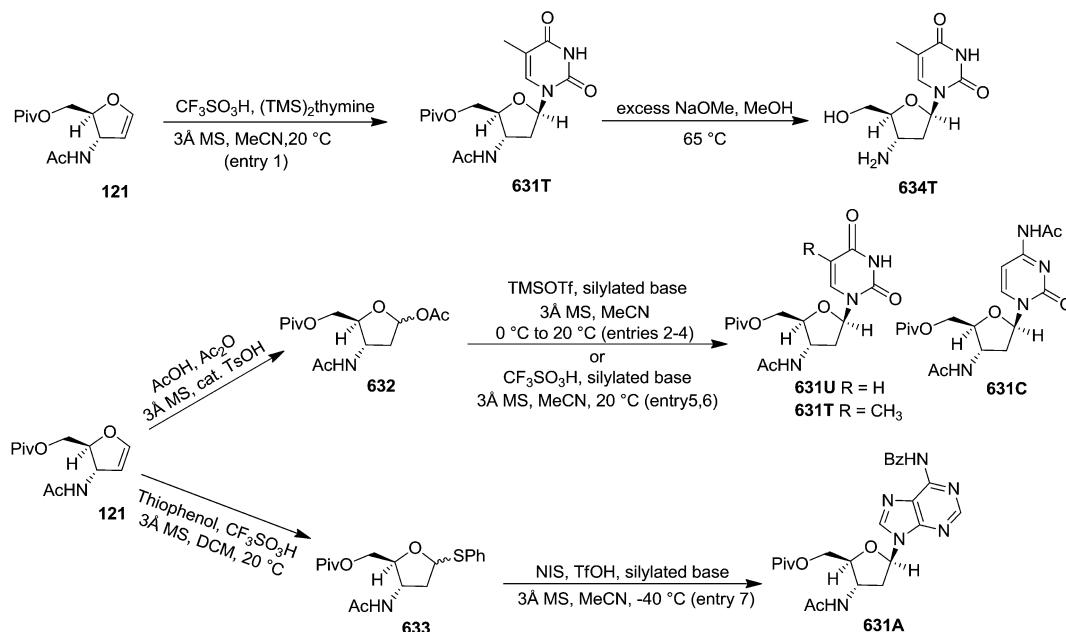
isopropylidene-*manno* furanose³¹ and 2,3-*O*-isopropylidene-*lyxo*-furanose³⁰ respectively.¹⁰ These glycals (139 and 132c) on treatment with PhSeCl in presence of AgOTf followed by glycosylation with pyrimidine bases in non polar solvents accomplished 2'-deoxy-2'-phenylselenenyl nucleosides 613-615. In all cases, removal of the phenylselenenyl group was carried out by reaction with *n*Bu₃SnH in refluxing toluene to afford 2'-deoxy-nucleosides 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



Scheme 108

with crude furanoid glycal in the presence of $\text{Pd}_2(\text{dba})_3$ 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 $(\text{TMS})_2\text{thymine}$ 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 $\text{CF}_3\text{SO}_3\text{H}$ 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 $\text{CF}_3\text{SO}_3\text{H}$ as the activating agent (Table 12, entries 5 and 6); possibly $\text{CF}_3\text{SO}_3\text{H}$ 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 $\text{CF}_3\text{SO}_3\text{H}$ 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**.

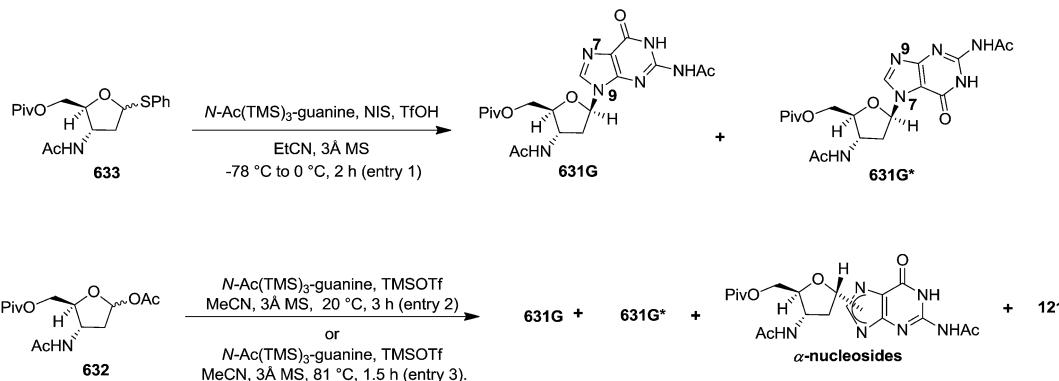
In the case of guanine glycosylations, the reaction of **633** under kinetic conditions gave primarily the N-7 regioisomer **631G*** as the major nucleoside product (Scheme 109, Table 13,

Table 12 Glycosylation of **121** to 3'-amido-2',3'-dideoxynucleosides^a

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

^a (Method a) $\text{CF}_3\text{SO}_3\text{H}$, 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) $\text{CF}_3\text{SO}_3\text{H}$, 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).





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.

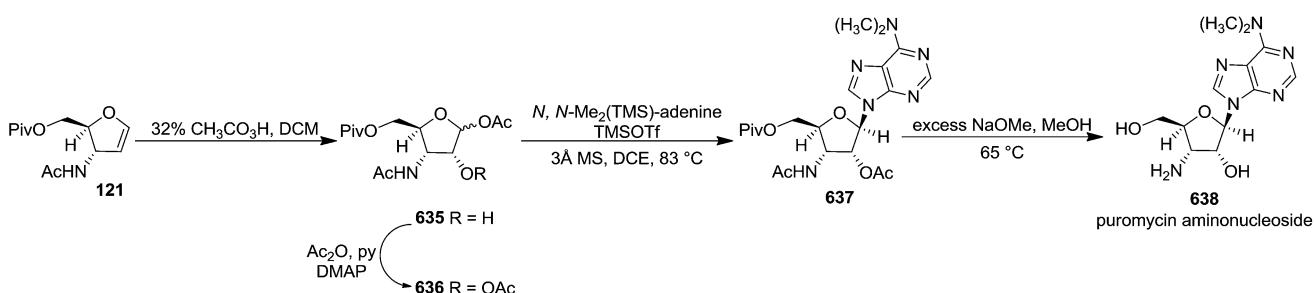
Peroxyacetic acid epoxidation followed by acetylation of 3-trifluoroacetamide glycal 122 furnished diacetate 640 *via* 639 (Scheme 111). Under the thermodynamic conditions of these glycosylations, the naturally occurring N-9 regioisomers 641A, 641G, and 641A' were the major products (Table 14, entries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

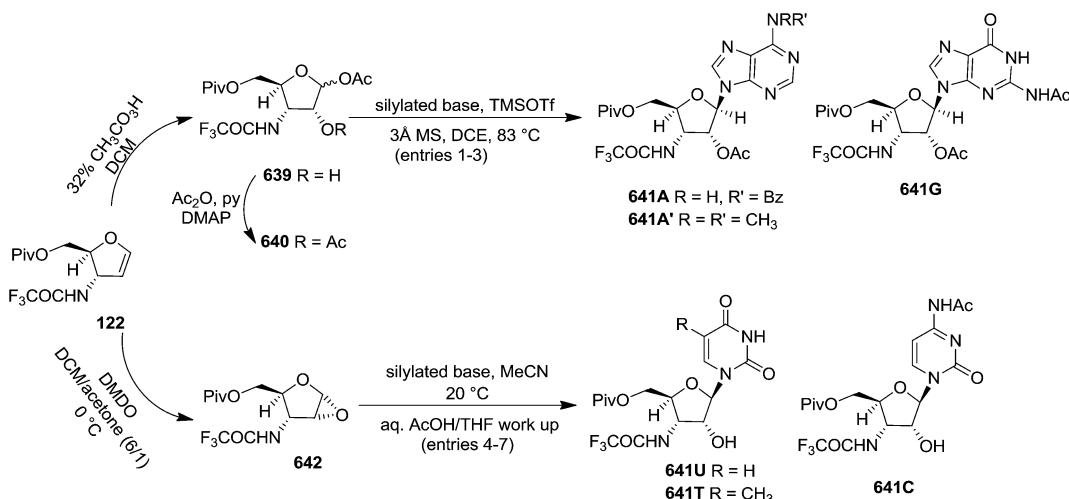
In 1997, Castillón *et al.* also reported the formation of 2',3'-dideoxy nucleosides by electrophilic addition of selenium to furanoid glycal 610, which was synthesized from 2-deoxyribose 67.⁸¹ They further discussed the synthesis of d4T 577 *via* precursor 656 through selenium-mediated glycosylation and selenoxide elimination.

Thus, 2-deoxyribose 67 was converted into the phenyl-1-seleno-glycoside 645 (mixture $\alpha/\beta = 1.9 : 1$) in four steps involving methyl glycoside synthesis, selective 5-OH protection, Barton deoxygenation, and treatment with PhSeH in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. Oxidation of 645 gave glycal 610 with a yield of 52%. The reaction of glycal 610 with (TMS)₂uracil, 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)₂thymine 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 ($\beta/\alpha = 89 : 11$) was obtained in a yield of 78% (Scheme 112).



Scheme 110



Scheme 111

Table 14 Epoxidation/glycosylation of 122 to 3'-amido-3'-deoxynucleosides^a

Entry	Silylated base	Glycosyl donar	Conditions	Nucleoside, isolated yield
1	<i>N</i> -Bz(TMS) ₂ -adenine	640	a	641A, 90%
2	<i>N</i> -Ac(TMS) ₂ -guanine	640	a	641G, 77% (10 : 1)
3	<i>N,N</i> -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	<i>N</i> -Ac(TMS) ₂ -cytosine	642	b	641C, 71%
7	<i>N</i> -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).

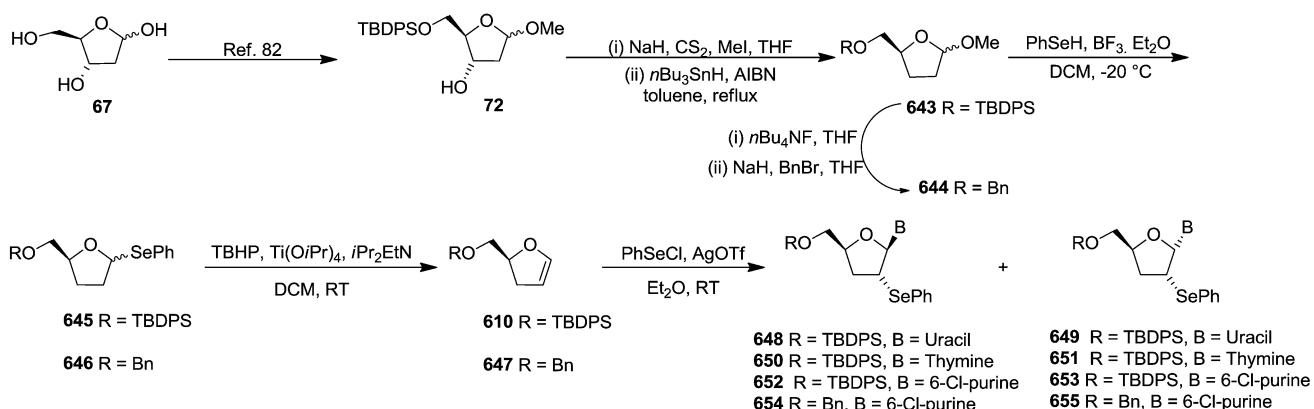
In the same year, this group also reported stereoselective synthesis of 2'-deoxy-2'-phenylselenenyl nucleosides from furanoid glycals in a “one pot” reaction and efficiently converted

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)₂uracil 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).

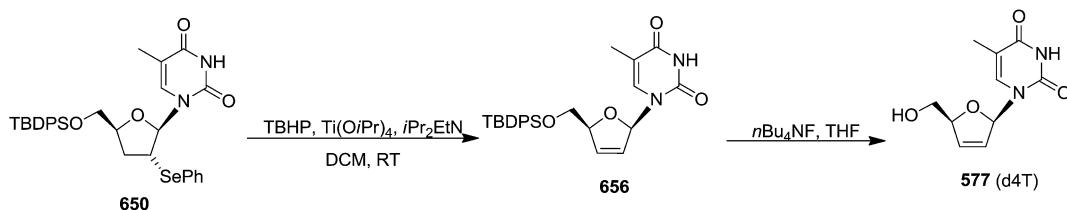
Under the identical reaction condition treatment of glycal 214 and 132c afforded 2'-deoxy-2'-phenylselenenyl nucleosides β -gluco 658/ α -gluco 659 (86 : 14) in 95% yield and β -xylo 614/ α -xylo 660 (91 : 9) in 91% yield respectively (Table 15, entries 2 and 3).

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 -lactone¹⁸ and 71a, 90, 663, 664 and 66j from 2-deoxyribose.^{24,28} For the glycals (661, 662, 66e, 71a,

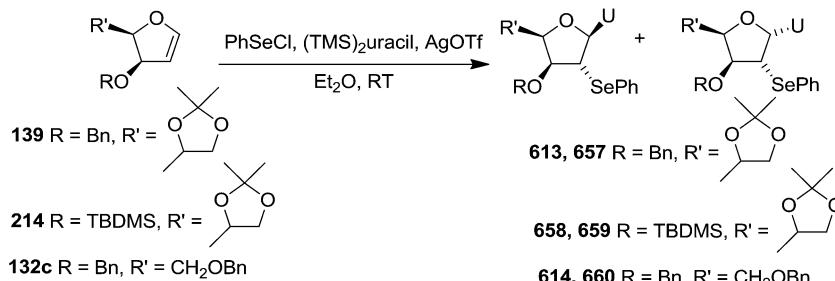


Scheme 112





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 ¹H NMR spectrum of the reaction mixture.

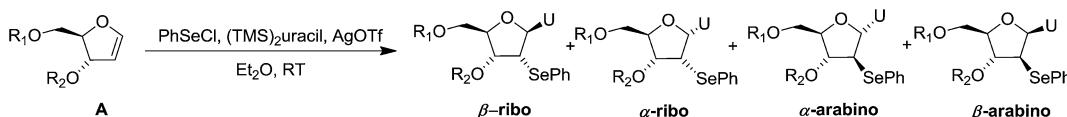
90, 663, 664, 665 and 66j) with an *erythro* configuration, stereoselectivity was seen to depend on the protecting groups at positions 3 and 5 (Scheme 115, Table 16).

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*Bu₃SnH 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-glucos 136a configured furanoid 1,2-diols respectively on

treatment with I₂/PPh₃/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 coworkers 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 (N₂C(CO₂Et)₂ : Rh₂(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

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 666a R ₁ = OH, R ₂ = Bn	14	—	49	—
662 R ₁ = TBDMS, R ₂ = Bn	1.5	87	667 R ₁ = TBDMS, R ₂ = Bn 667a R ₁ = OH, R ₂ = Bn	32	16	16	—
66e R ₁ = TBDMS, R ₂ = TBDMS	1.5	88	668 R ₁ = TBDMS, R ₂ = TBDMS 668a R ₁ = OH, R ₂ = TBDMS	28	21	15	—
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 670a R ₁ = TBDPS, R ₂ = Bn, R = SePh ^b	44	9	—	—
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 672a R ₁ = TBDPS, R ₂ = MEM, R = SePh ^b	54	18	15	4
665 R ₁ = Ac, R ₂ = TBDPS	2	84	673 R ₁ = Ac, R ₂ = TBDPS 673a R ₁ = Ac, R ₂ = TBDPS, R = SePh ^b	23	14	16	6
66j R ₁ = TBDPS, R ₂ = TBDMS	2	87	674 R ₁ = TBDPS, R ₂ = TBDMS	66	20	14	—

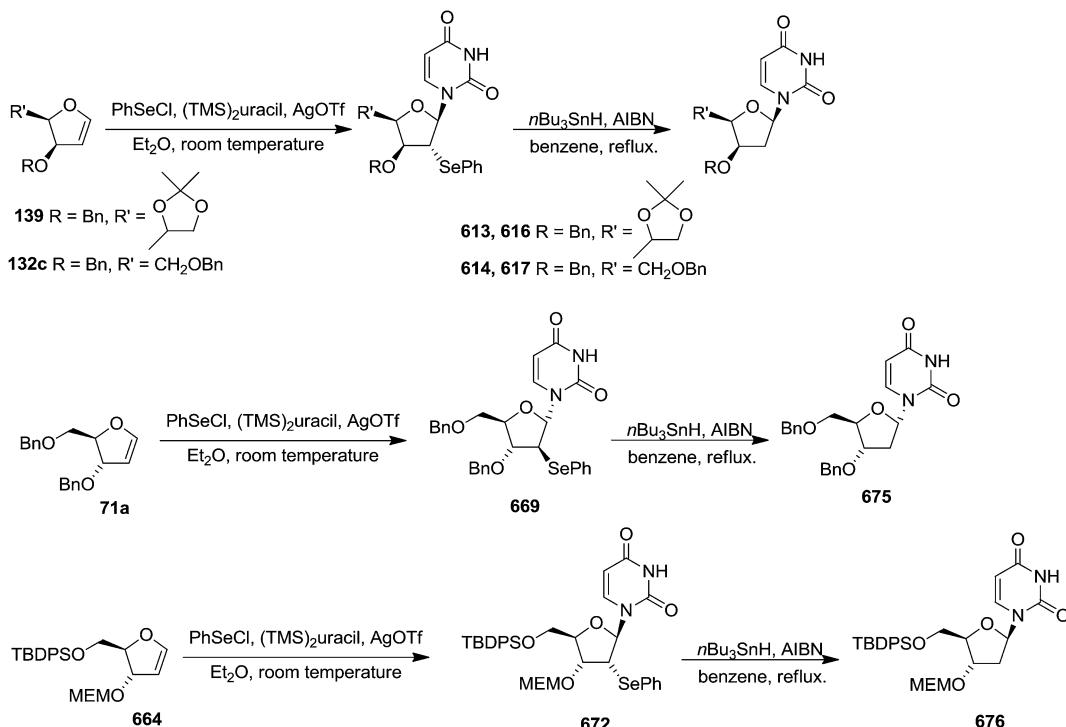
^a Reactions were carried out at room temperature using the molar ratio glycal/PhSeCl/AgOTf/Uracil(TMS)₂ = 1/1.5/1.7/2. ^b R = SePh stands for selenenylation of nucleosides at position 5.

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 derived⁷⁹ (*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

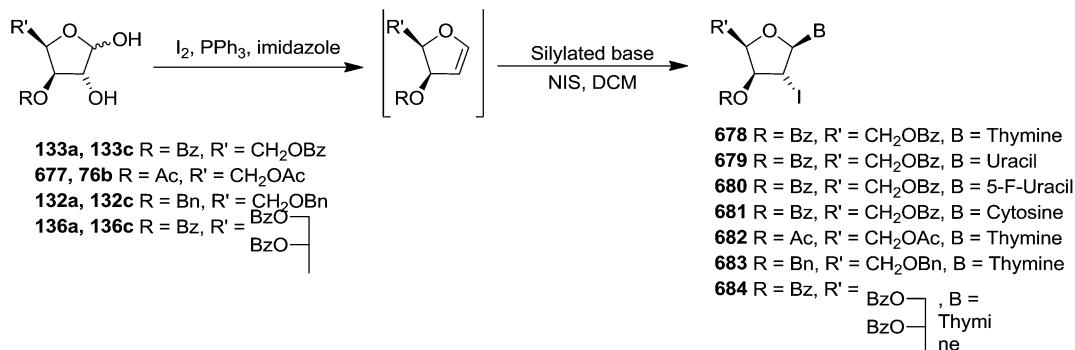
vacuum pyrolysis in a Kugelrohr apparatus afforded **693** and **270** respectively (Scheme 119). Also, exposure of the lithium derivative of **693** to excess *n*Bu₃SnCl afforded **694** in 60% yield. They also treated **270** with KO'Bu in the presence of PhSCl and PhSeCl to afford **695** and **696** 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 BF₃·Et₂O to give the desired epimeric mixture of carbinols, *i.e.*

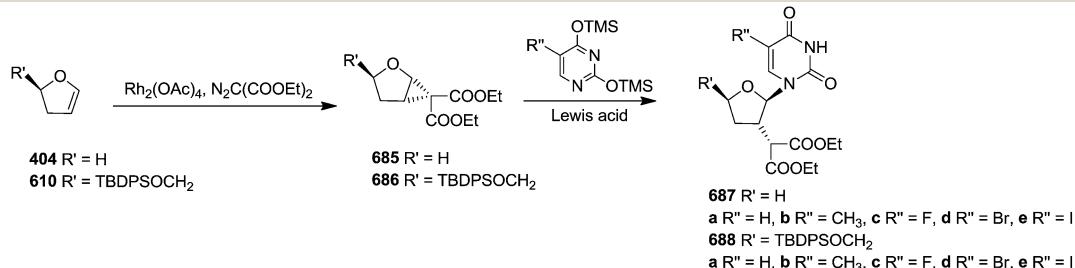


Scheme 116

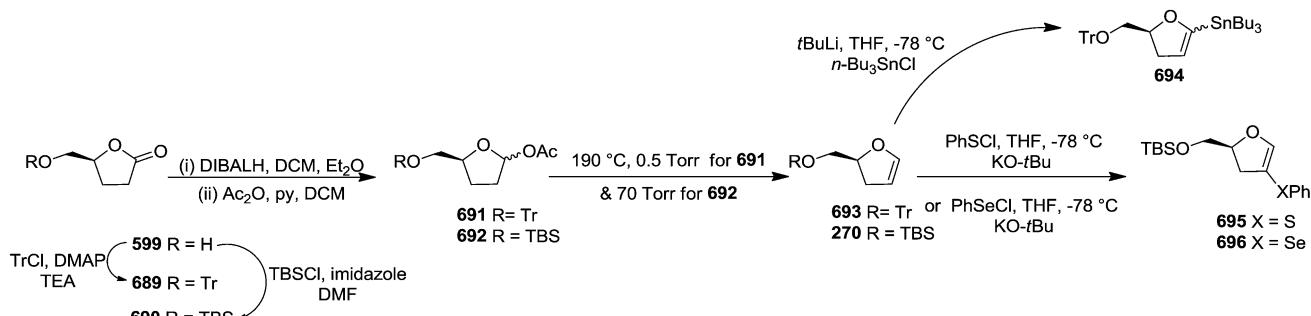




Scheme 117



Scheme 118



Scheme 119

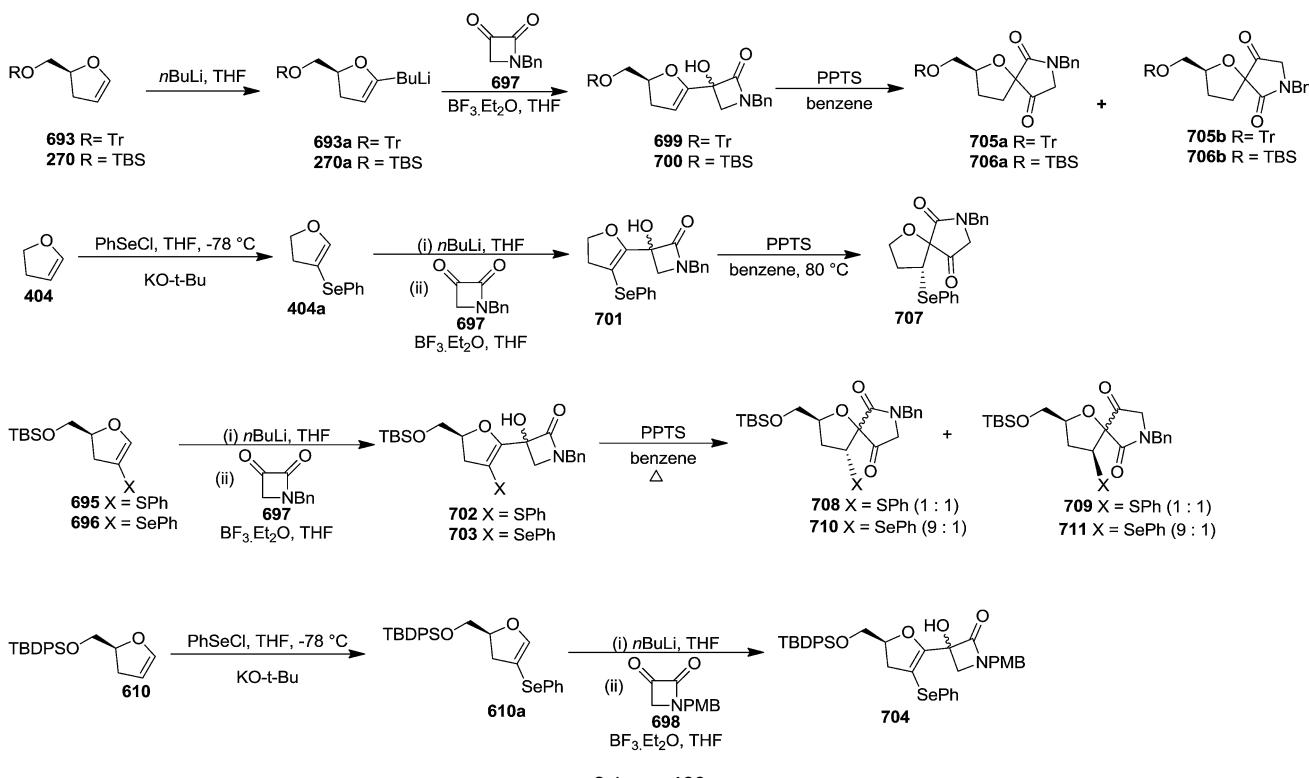
(699–704) respectively. Treatment of (699–703) with pyridinium *p*-toluenesulfonate (PPTS) in benzene afforded spirocyclic keto amides (705, 706, 707, 708, 709, 710, 711) respectively (Scheme 120).

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 $(\text{NH}_4)_2\text{SO}_4$ followed by benzylation with BnBr of the resulting 65a. Then they applied Miethchen method⁸⁸ 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 ($n\text{Bu}_3\text{SnH}$, AIBN). Addition of $(\text{TMS})_2\text{uracil}$ to 714 in the presence of TMSOTf furnished a 4 : 1 mixture of isomeric nucleosides in 76% yield. The major one was 715 α (NMR) whose hydrogenolysis afforded 2'-deoxy-2'-difluoromethyluridine 716 α (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 $(\text{TMS})_2\text{uracil}$ gave a 57 : 43 mixture of 715 β and 715 α isomers (NMR), respectively, via a $\text{S}_{\text{N}}2$ type reaction. Finally, the deprotection of the benzyl groups was easily achieved by hydrogenolysis of 715 β and 715 α to give the two desired nucleosides 716 β and 716 α with good yields (Scheme 122, method B).

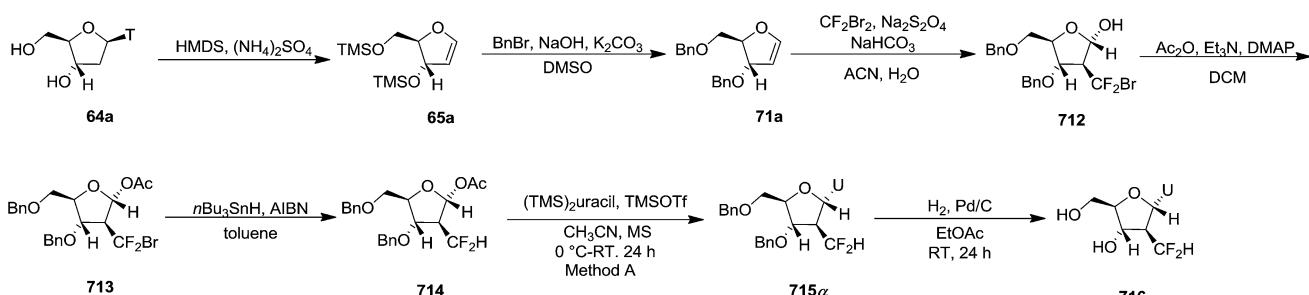
In 2005, Choudhury and Pierce *et al.* synthesized D-D4FC 724 from an aromatization prone xylo-furanoid glycal 721, by development of a palladium mediated Ferrier rearrangement-type glycosidation.⁸⁹ For the synthesis of xylo-furanoid glycal 721, they chose commercially available 1,2-isopropylidene D-(+)-xylofuranose 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 $\text{I}_2/\text{resin bound Ph}_3\text{P}/\text{imidazole}$ afforded xylo-furanoid glycal 721 in more than 90% yield. After several trial and error for the choice of solvent, base and



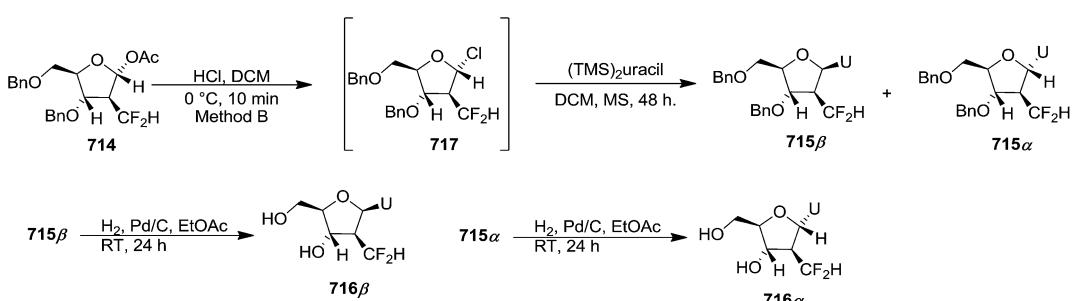
Scheme 120

different mol% of Pd(Ph₃P)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(Ph₃P)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

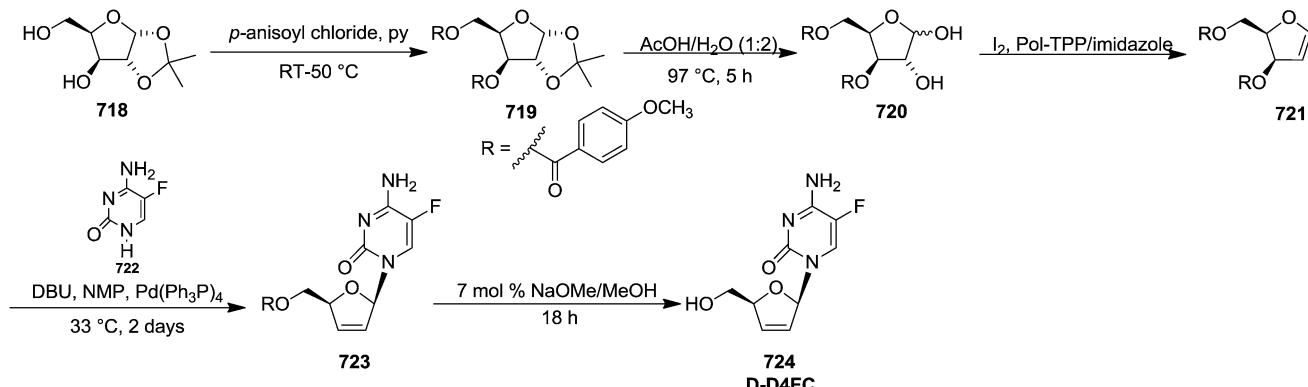


Scheme 121

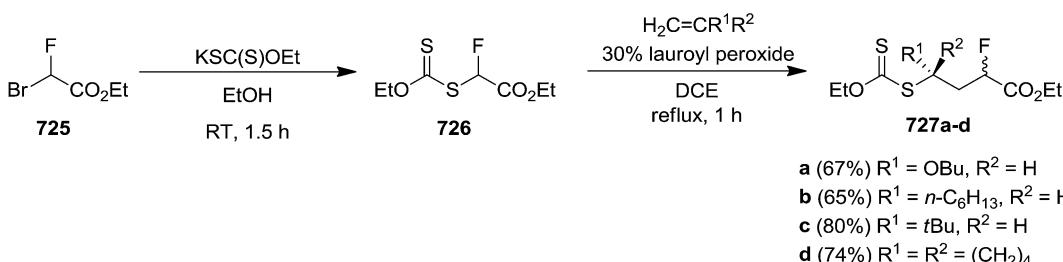


Scheme 122

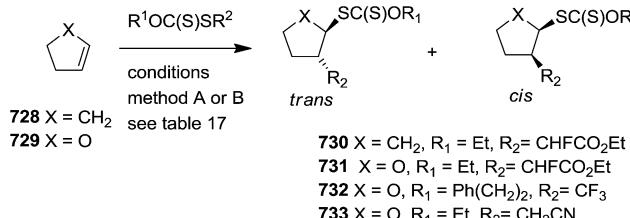




Scheme 123



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

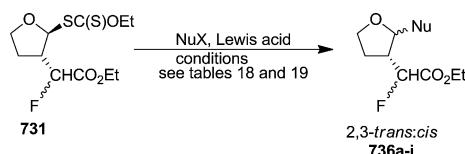
Then they studied the ethyl fluoroacetate group transfer reaction with the slow addition of lauroyl peroxide (30%) over 1 h in the mixture of different terminal alkenes (1.1 equiv.) and xanthate 726 in refluxing DCM (Scheme 124) to form fluoroesters (727a–d) in fair to good yields as a mixture of diastereomers (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 (%)	<i>Trans/cis</i> dr	Product
1	X = CH ₂	726: $R^1 = Et$, $R^2 = CHFCO_2Et$	A	79	>98 : 2	730
	X = O		B	67		
2	X = O	726	A	81	>98 : 2	731
	X = O		B	73		
3	X = O	734: $R^1 = Ph(CH_2)_2$, $R_2 = CF_3$	A	30	>98 : 2	732
	X = O		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 Et₃B, DCM, room temperature, 1–2 h. ^b Stirring was maintained overnight at room temperature.



Scheme 126

peroxide was added slowly to a mixture of alkene and xanthate (method A). In case of cyclopentene ($X = \text{CH}_2$) 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 ($X = \text{O}$) 729 and xanthate 726, and a mixture of two *trans* diastereomers of 731 (2,3-*trans* disubstituted tetrahydrofuran derivatives, $^1\text{H}\{^{19}\text{F}\}$ 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_3B , 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 $(\text{TMS})_2\text{thymine}$ 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.

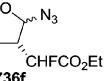
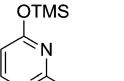
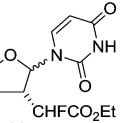
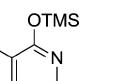
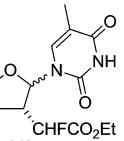
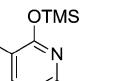
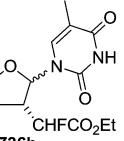
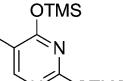
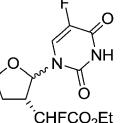
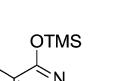
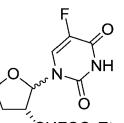
The synthesis of furanoid glycals (171, 173) proposed by Haraguchi and group has been already discussed in Scheme 30.³⁸ Now, the utilization of their synthesized furanoid glycals (66e, 171 and 173) is being discussed here for the synthesis of 2'-deoxynucleosides and its 1'-branched analogues. They performed NIS-mediated electrophilic glycosidation between protected *erythro*-furanoid glycals (66e, 171 and 173) and silylated thymine in $\text{CH}_3\text{CN}/\text{DCM}$ 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 (740 α , 62% yield)

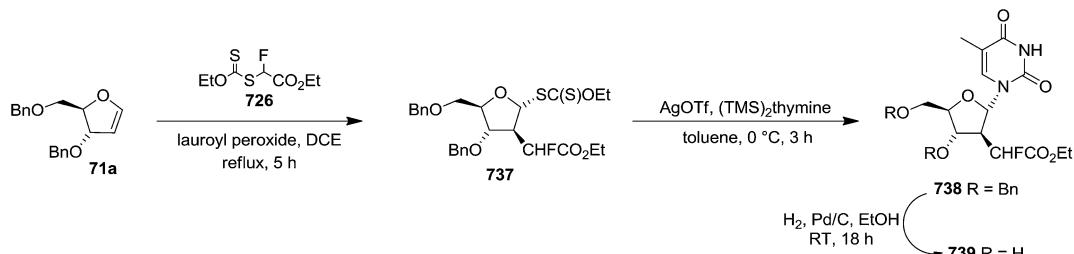
Table 18 Carbon–oxygen and carbon–carbon bond formation

Entry	Nu-X	Conditions	Lewis acids	Products	Yields (%)	Trans/cis dr
1	EtOH	Toluene, 20 °C, 15 min	AgOTf		72	7 : 3
2	tBuCH ₂ OH	Toluene, -17 °C, 1 h	AgOTf		73	3 : 2
3	Me ₃ SiCN	Toluene, -78 °C, 2.5 h	SnCl ₄		83	9 : 1
4	BnO-C(=O)OSiMe ₃	Toluene, -17 °C, 2 h	AgOTf		36	4 : 1
5		Toluene, -17 °C, 1 h	AgOTf		32	>98 : 2



Table 19 Carbon–nitrogen bond formation

Entry	Nu-X	Conditions	Lewis acids	Products	Yields (%)	Trans/cis dr
1	Me ₃ SiN ₃	Toluene, -17 °C, 1 h	AgOTf		68	3 : 2
2		Toluene, -17 °C, 2 h	AgOTf		63	9 : 1
3		Toluene, -17 °C, 1.5 h	AgOTf		83	9 : 1
4		Toluene, -17 °C, 4 h	Cu(OTf) ₂		76	9 : 1
5		Toluene, -17 °C, 1.5 h	AgOTf		45	4 : 1
6		Toluene, -17 °C, 3.5 h	Cu(OTf) ₂		25	4 : 1



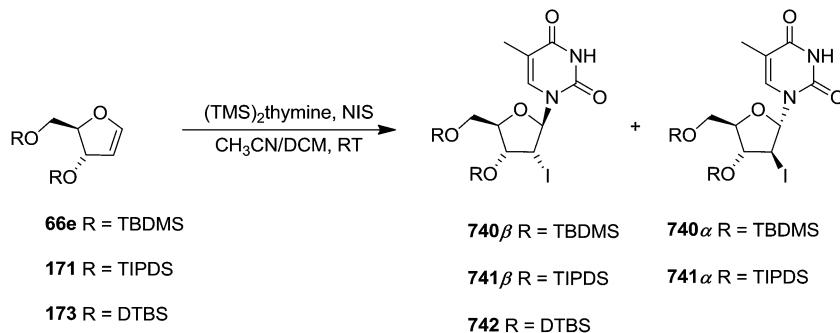
Scheme 127

dominated over that of the β -anomer (**740 β** , 15% yield) in the case of glycal **66e**. On the other hand, glycal **171** gave equal amounts of the β -(**741 β** , 35% yield) and α -(**741 α** , 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^9 -(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 $n\text{Bu}_3\text{SnH}$, $\text{Et}_3\text{B}/\text{O}_2$ 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 *t*BuLi (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*-



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	740 β and 740 α (77%)	1 : 4
2	171	741 β (35%) and 741 α (35%)	1 : 1
3	173	742 (76%)	—

^a All reactions were carried out in CH₃CN/DCM at rt for 12 h by using (TMS)₂thymine (3.0 equiv.) and NIS (1.5 equiv.).

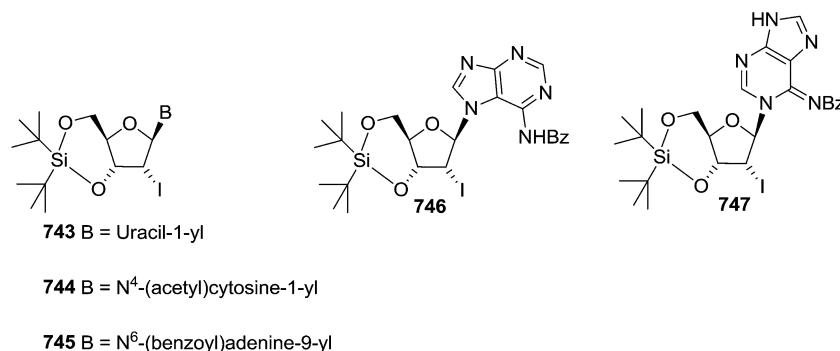
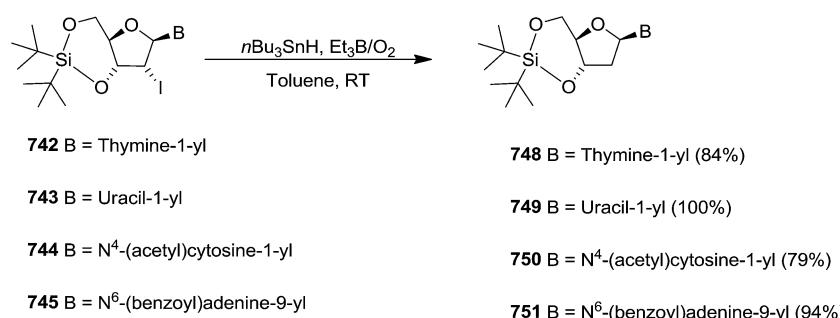


Fig. 6 Compounds (743–747).



Scheme 129

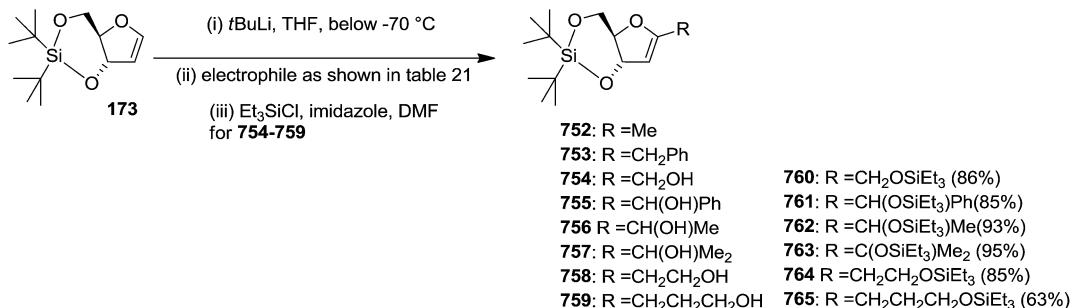
furanoid glycals (754–759). To obtain derivatives suitable for glycosidation, 1-(ω -hydroxy)alkyl *erythro*-furanoid glycals (754–759) were converted to their *O*-triethylsilyl derivatives (760–765) respectively on silylation (Scheme 130).

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*Bu₃SnH, Et₃B/O₂, 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





Scheme 130

Table 21 Preparation of 1-alkyl and 1-(omega-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)	$\text{CH}(\text{OH})\text{Ph}$	755 (93%) ^c
5	MeCHO (5)	$\text{CH}(\text{OH})\text{Me}$	756 (90%) ^c
6	CH_3COCH_3 (5)	$\text{C}(\text{OH})\text{Me}_2$	757 (19%) ^d
7	Ethylene oxide (5) & $\text{BF}_3 \cdot \text{OEt}_2$ (5)	$\text{CH}_2\text{CH}_2\text{OH}$	758 (62%)
8	Trimethylene oxide (5) & $\text{BF}_3 \cdot \text{OEt}_2$ (3)	$\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	759 (65%)

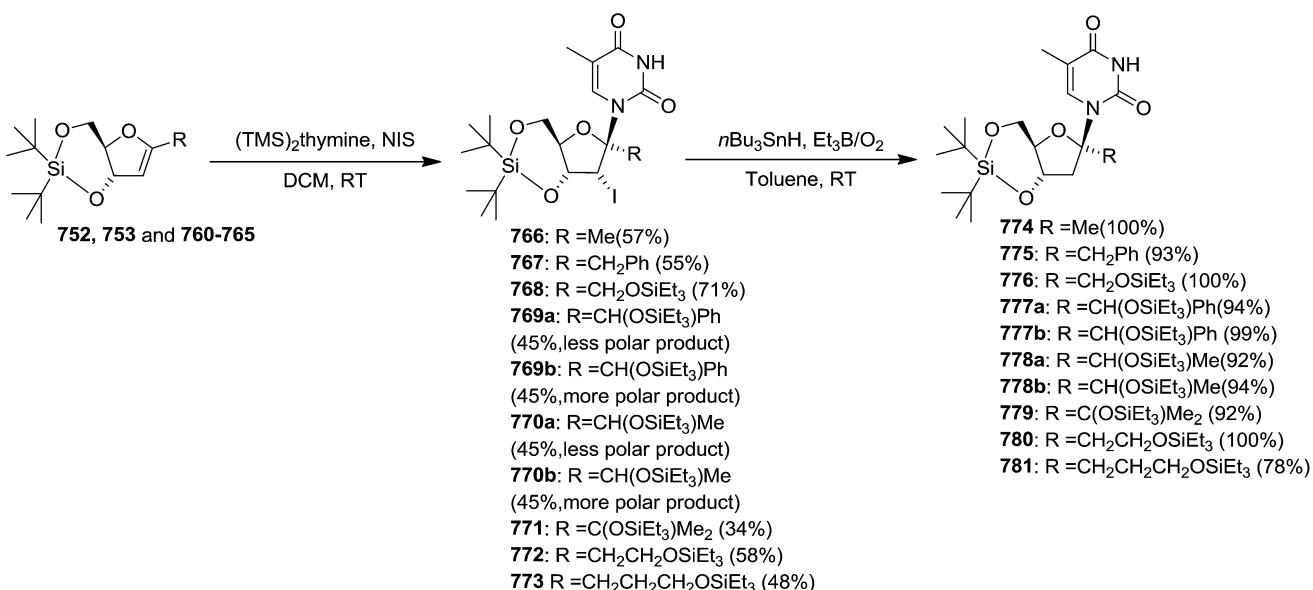
^a After addition of the respective electrophile, the reaction mixture was stirred below -70°C for 0.5 h, except entry 2. ^b After addition of the electrophile, the reaction mixture was stirred at -40°C for 11 h. ^c The product was obtained as a mixture of diastereomers. ^d The starting material (173) 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 $(\text{TMS})_2\text{thymine}$ (2.0 equiv.) in the presence of NIS (2.5 equiv.) in dry DCM at $-30^\circ\text{C} \rightarrow \text{rt}$ 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 $n\text{Bu}_3\text{SnH}$ 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



Scheme 131

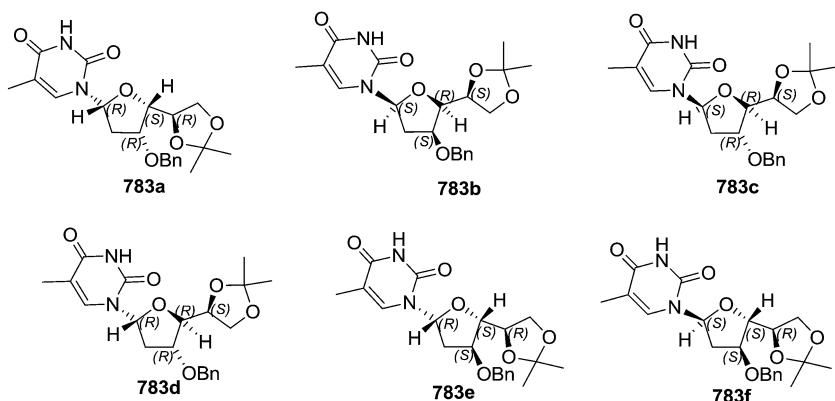
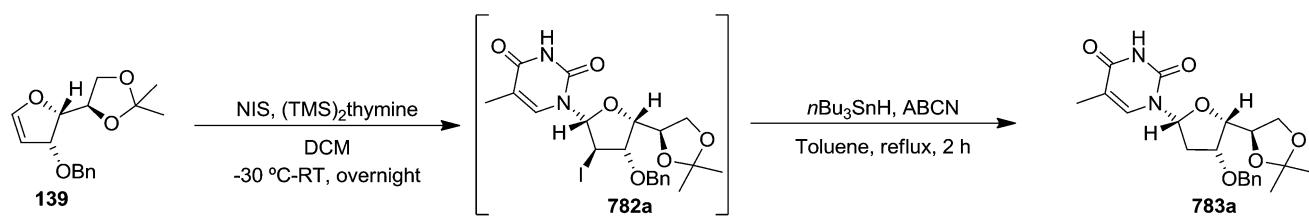
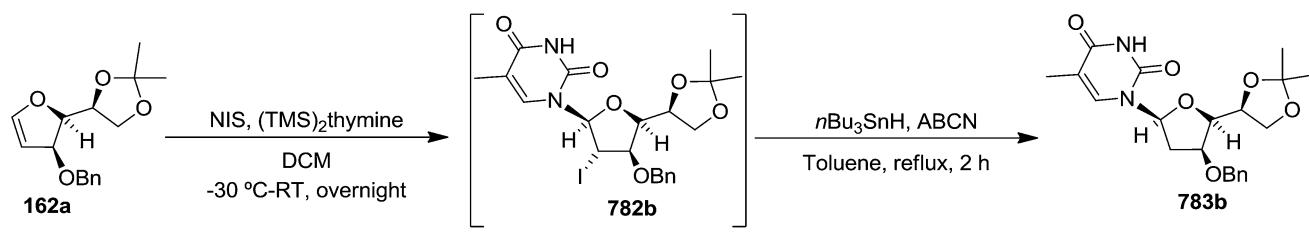


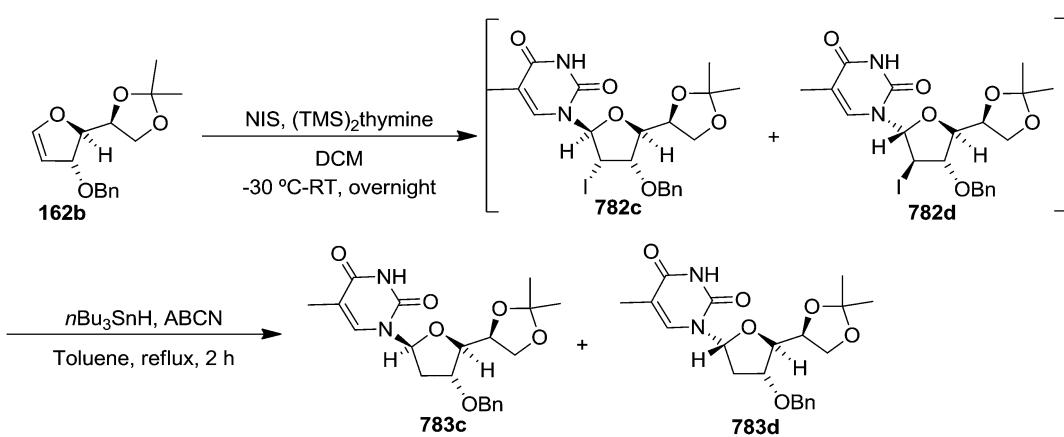
Fig. 7 Structures of 2'-deoxynucleoside analogues (783a–f).



Scheme 132



Scheme 133

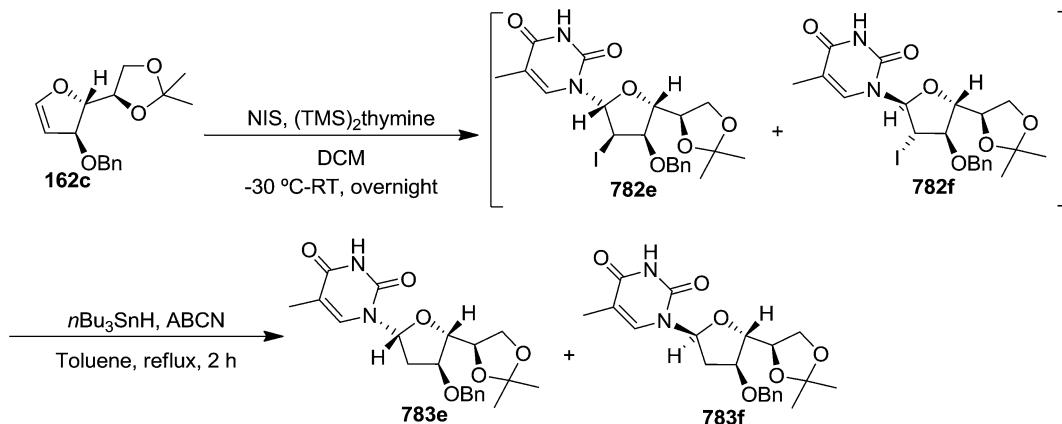


Scheme 134

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%





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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