Chemistry of Glycosyl Fluorides

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Abstract: In recent years glycosyl fluorides have been utilized as versatile sugar donors in the field of organic synthesis including natural product synthesis as well as carbohydrate chemistry. We describe here an update on developments in the preparation and the utility of C–O, C–C, C–N, and C–S bond formations, including total syntheses of natural products.

Key words: glycosyl fluoride, preparation of glycosyl fluoride, C–C or C–X bond formation, total synthesis of natural products

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1. Introduction

Glycosyl fluorides have drawn much attention in the field of biochemistry due to their potential biological activity. Several substituted glucosyl fluorides were found to be enzyme inhibitors.[1] In recent years extensive studies have shown that they are not only useful biological probes but also versatile substrates for the glycosidation reaction.

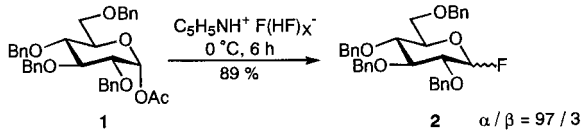
Glycosyl halides have been utilized as glycosyl donors in organic chemistry. Glycosyl bromide, chloride, and sometimes iodide have been used with various activators for the anomeric carbon to act as an electrophile in glycosidic bond formation. Since 1981 glycosyl fluorides have been utilized for effective glycosylation reactions[2] because of their enhanced stability, ease of handling, and higher stereoselectivity compared with other glycosyl halides. This paper provides an update on the recent advances in the chemistry of glycosyl fluorides during the last decade.

2. Preparation of Glycosyl Fluorides

Many studies for preparing the glycosyl fluorides have led to the development of useful fluorination reagents. In this section, each reagent is discussed separately.

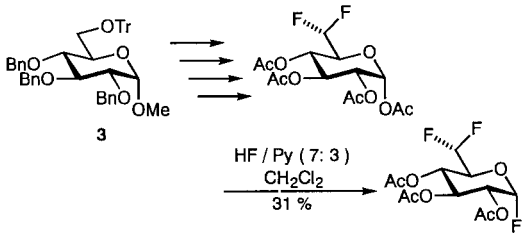
2.1 Hydrogen Fluoride

Hydrogen fluoride has been applied to fluorination of acetylated sugar derivatives. First, both 1-unprotected and *O*-acetylated sugars were converted to the corresponding 1-fluoro derivatives using a 50 to 70% hydrogen fluoride/pyridine mixture [pyridinium poly(hydrogen fluoride)] (HF/Py).[3] Compared with l-unprotected sugars, the *O*-acetylated sugars preferentially underwent the fluorination. The reaction of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucose (**1**) with this reagent afforded the desired glycosyl fluoride in 89% yield with α-selectivity (Scheme 1).



Scheme 1

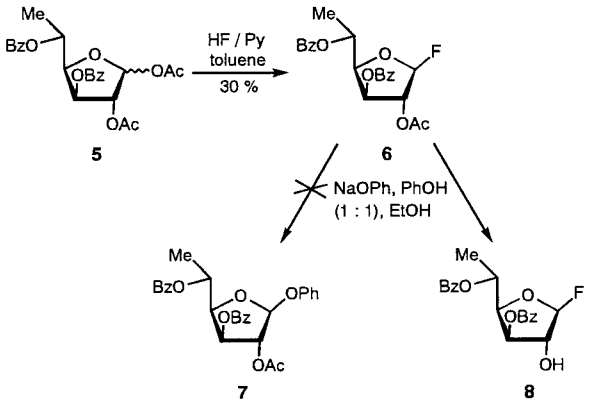
With this reagent, 6-deoxy-6,6-difluoro- α-D-glucopyranosyl fluoride (**4**), which is a derivative of an enzyme inhibitor, was synthesized from methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside (**3**) for its use in inhibition studies[4] (Scheme 2).



Scheme 2

In the field of furanoses, the synthesis of the glycosyl fluoride **6** was performed by treatment of the acetylated sugar **5** with HF/Py.[5] It was envisioned that it would be converted into an intermediate **7** of the model compound of an antibiotic agent. However, the treatment of **6** with 1

eqivalent each of PhONa and PhOH gave only the deacetylated compound **8** in place of the desired **7** (Scheme 3).



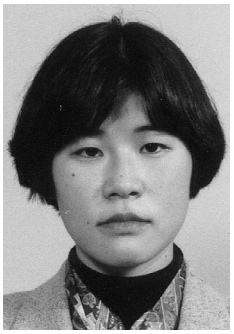
Scheme 3

Further, *N*-glycosyl triazole derivatives devised as a new glycosyl donor, were reacted with hydrogen fluoride/pyridine for preparing the corresponding glycosyl fluorides[6,7] (Scheme 4). This method resolved many difficulties encountered in the usual approaches.

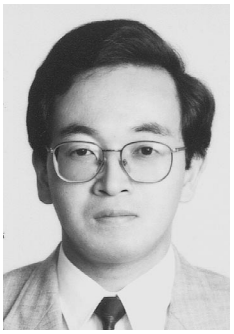
DAST (diethylaminosulfur trifluoride) is known as the best reagent for fluorination reacts with sugar hemiacetals to give the glycosyl fluorides in good yield, but it is relatively expensive. Even the reaction between acyl glycosides and HF/Py incurs some problems. While this reagent is preferable to anhydrous HF, a large excess is needed to complete the reaction. Therefore, it is not suitable for acid-sensitive sugar derivatives. From a synthetic point of view, this procedure using the triazole derivative can be a good method for glycosilation due to the low temperature and use of small excess of the reagent.

Treatment of the triazole **9** derived from the corresponding azide with HF/Py complex furnished the correspond-

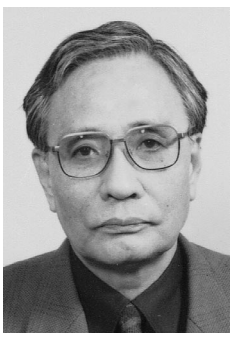
Biographical Sketches



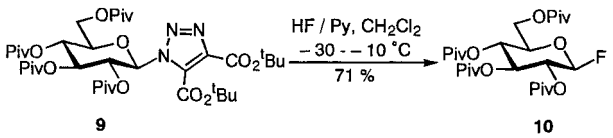
Miyuki Shimizu was born in Tokyo in 1974 and graduated from the Faculty of Science of Chiba University in 1996. At present she is a student of a masters course in the Graduate School of Science and Technology of Chiba University. Her research interests are in organonucleic acid chemistry.



Hideo Togo was born in Ibaraki in 1956. He completed his doctoral thesis in 1983 under the supervision of Professor Shigeru Oae in Tsukuba University. He then became a postdoctoral fellow at University de Lausanne (Professor Manfred Schlosser) in Switzerland (1983–1984) and then at ICSN of CNRS (Professor Derek H. R. Barton) in France (1984–1985). He became a research associate at Tsukuba University in 1987 and then at the present University in 1989. He has been an associate professor since 1994. His research interests are free radical reactions and their synthetic uses with hypervalent iodine and silicon compounds for organic synthesis.

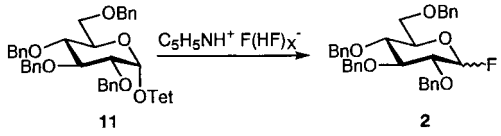


Masataka Yokoyama was born in Formosa in 1935 and graduated from Ibaraki University in 1958. He obtained his PhD from Tokyo Metropolitan University (Professor Kazuo Hata) in 1972. He spent a year as a postdoctoral fellow under Professor D. C. Dittmer at Syracuse University in 1975. He was visiting professor of Nijmegen University and North Eastern Hill University. Since 1985 he has been full professor of organic chemistry at Chiba University. His research interests are organonuceic acid chemistry, sugar chemistry and heterocyclic chemistry.



Scheme 4

ing glycosyl fluoride **10** with a β-configuration. In this reaction, the ratio of the α- and β-anomers of the resultant fluoride depends on the protecting group and on the reaction conditions. As a glycosyl donor, (1-phenyl-1*H*-tetrazol-5-yl)glycoside was prepared to be transformed into the corresponding fluoride with hydrogen fluoride/pyridine[8] (Scheme 5, Table 1).

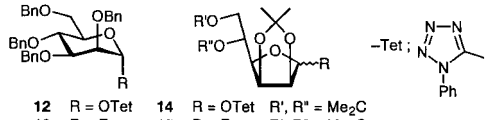


Scheme 5

Table 1. Reaction of OTet Glycosides with HF/Pyridine

Entry	OTet Glycoside (α-D/β-D)	Equiv	Temp (°C)	Time (min)	Glycosyl Fluoride[a] (α-D/β-D)	Yield (%)
1	**11** (100:0)	160	0	30	**2** (90:10)	95
2	**11** (82:18)	5	0	10	**2** (88:12)	89
3	**11** (63:37)	5	0	10	**2** (57:43)	90
4	**12** (100:0)	10	0	10	**13** (100:0)	76
5	**14** (100:0)	5	0	3	**15** (100:0)	46
					16 (100:0)	12
6	**14** (100:0)	5	–20	10	**15** (92:8)	72
					16 (100:0)	10

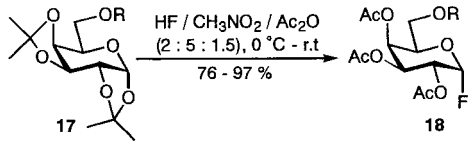
a



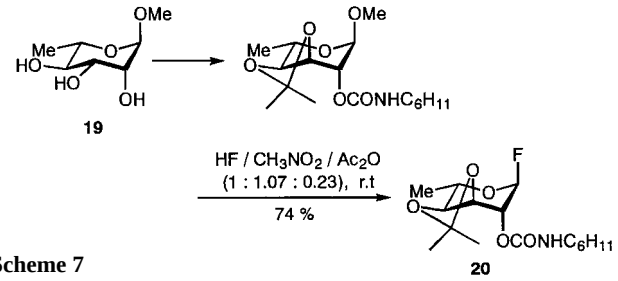
12 R = OTet **13** R = F **14** R = OTet R', R" = Me_2C **15** R = F R', R" = Me_2C **16** R = F R' = H R" = H

By the use of HF/Py, benzylated-D-glucopyranoside **11** and α-D-mannopyranoside **12** could be converted into the corresponding fluorides **2** and **13** in good yields, respectively. The stereoselectivity seems independent of the anomeric configuration of OTet glycosides, but is dependent on the reaction conditions. The reaction of α-D-mannofuranoside **14** bearing an acid-sensitive group with 5 equivalents of HF/Py at 0 °C for 3 minutes gave the corresponding fluoride **15** (46%) along with the diol **16** (12%). When the reaction was performed at lower temperature, the yield of **15** increased to 72%.

On the other hand, by using a homogeneous reagent/catalyst/solvent combination, the synthesis of 6-*O*-substituted 2,3,4-tri-*O*-acetyl- α-D-galactopyranosyl fluorides **18** was carried out from 6-*O*-substituted 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoses **17**.[9] (Scheme 6). When pivalic anhydride was chosen as the solvent in place of acetic anhydride, *O*-pivaloyl protected glycosyl fluoride was obtained. In addition, after the free hydroxyl groups of α-L-rhamnopyranoside **19** were modified, α-L-altropyranosyl fluoride **20** was obtained in 74% yield by using this reagent ($HF/MeNO_2/Ac_2O$)[10] (Scheme 7).



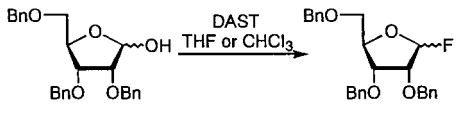
Scheme 6 R = Me, PhCO, $MeSO_2$ etc



Scheme 7

2.2 Diethylaminosulfur Trifluoride (DAST)

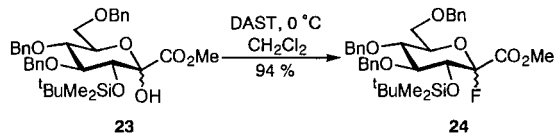
Since diethylaminosulfur trifluoride (DAST) was found as the best fluorinating reagent for a free anomeric hydroxyl group,[11] it has been utilized widely as the most preferable fluorinating reagent. The conversion of an alcohol to the corresponding fluoride is performed by exposure to DAST. In addition, it is noteworthy that the ratio of α/β of the glycosyl fluoride depends on the solvent. When 2,3,5-tri-*O*-benzyl-D-ribose (**21**) is allowed to react with DAST in THF, the anomeric ratio of the corresponding glycosyl fluoride **22** becomes 9:91. The α/β ratio becomes 20:80 with the use of $CHCl_3$ as the solvent[12] (Scheme 8).



THF ; α / β = 9 / 91
$CHCl_3$; α / β = 20 / 80

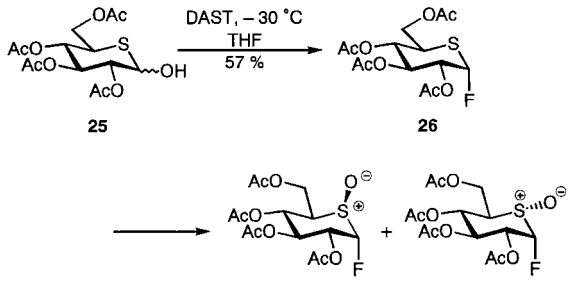
Scheme 8

The alcohol **23** was allowed to react with DAST easily to give the corresponding fluoride **24** in 94 % yield[13] (Scheme 9). Although the coupling of **24** with methanol was supposed to occur under the standard conditions, **24** was recovered intact.



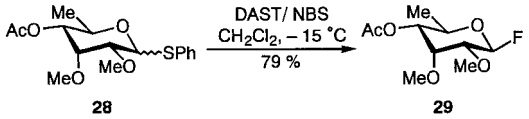
Scheme 9

The treatment of 2,3,4,6-tetra-*O*-acetyl-5-thioglucopyranose (**25**) with DAST gave the glycosyl fluoride **26** in 57% yield. The MCPBA oxidation of **26** afforded the corresponding sulfoxides with axial **27a** and equatorial **27b** isomers[14] (Scheme 10).



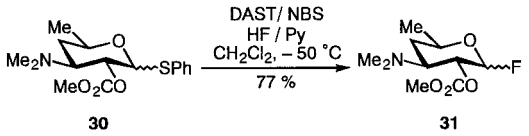
Scheme 10

Furthermore, the conversion of thioglycosides into glycosyl fluorides can be demonstrated by the treatment of DAST and NBS.[15] The reaction of phenyl thioglycoside **28** with the reagent (DAST/NBS) afforded the desired fluoride **29** in 79% yield[16] (Scheme 11).



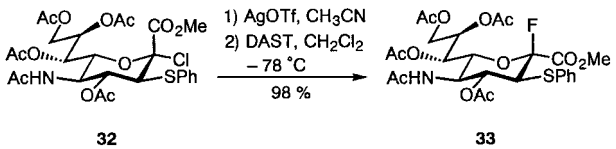
Scheme 11

On the contrary, the transformation of thioglycoside **30** into the fluoride **31** under the same conditions did not take place.[17] It was considered that the competitive attack of NBS to both the PhS and Me_2N groups led to the failure. In order to make a selective attack to the PhS group, HF/Py was added as a coactivator under the standard conditions at lower temperature to give the desired **31** in 77% yield (Scheme 12).



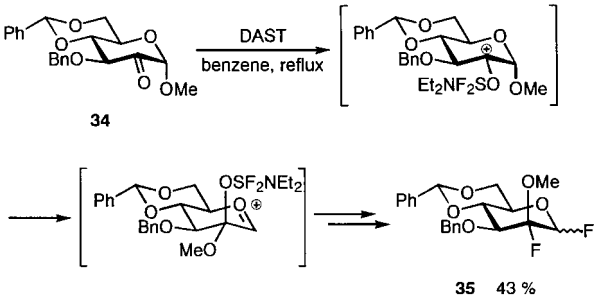
Scheme 12

The glycosyl fluorides can be also formed from glycosyl chlorides in two steps. At first, the direct transformation of the chloride **32** with AgF gave the desired fluoride **33** in 40% yield.[18] However, the chloride **32** when treated with AgOTf in MeCN followed by DAST in CH_2Cl_2 at –78 °C gave the fluoride **33** in 98% overall yield (Scheme 13).

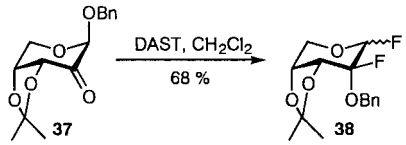


Scheme 13

Not only mono-fluorinated compounds but also *gem*-difluorinated compounds have received wide attention in the carbohydrate field. The *gem*-difluorinated compounds are synthesized by the treatment of 2-uloses with DAST. Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranoside-2-ulose (**34**) was allowed to react with DAST to give the compound **35** via the migration of the OMe group[19] (Scheme 14). When the β-anomer of **34** was used, methyl 4,6-*O*-benzylidene-2-deoxy-2,2-difluoro-3-*O*-benzyl derivative **36** was obtained. The 1,2-migration takes place only when the anomeric group has axial orientation. Similarly, *O*-benzyl derivative **37** was also converted to the desired *gem*-difluoro compound **38** in 68 % yield[20] (Scheme 14).



Scheme 14



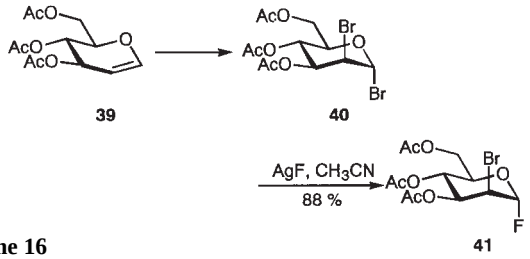
Scheme 15

Fluorination with DAST; General Procedure:[12]
To the alcohol (4.52 mmol) in a stirred solution of THF (12 mL) at –30 °C under argon gas was added DAST (1.2 equiv). After the cooling bath was removed, stirring at room temperature for 20 min completed the reaction. The reaction mixture was cooled to –30 °C and MeOH (0.3 mL) was added. The solution was neutralized with aq $NaHCO_3$ solution and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated to yield a crude mixture of fluorides which was separated by column chromatography (eluent; hexane/EtOAc, 2:1).

2.3 Metal Fluorides (MF_n)

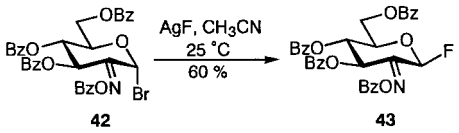
Metal fluorides have been employed to transform the glycosyl bromides and chlorides directly into glycosyl fluorides via the nucleophilic halide exchange. Silver fluoride is the most common fluorination reagent for this purpose. 3,4,6-Tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranosyl bromide (**40**) prepared in situ from the glycal **39** was allowed to react with AgF in MeCN to give a monofluori-

nated compound, 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranosylfluoride (**41**) stereoselectively in 88% yield[21] (Scheme 16). The same reaction was performed with benzoyloxyiminoglycosyl bromide **42** to give the β-fluoride **43** in 60% yield with the benzoyloxyimino group intact[22] (Scheme 17).



39 40 41

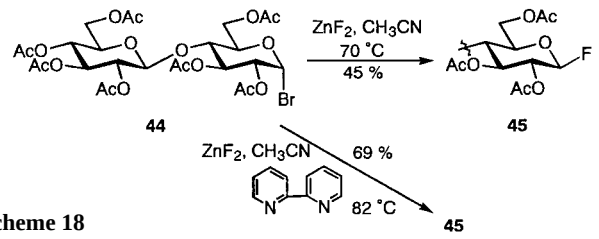
Scheme 16



42 43

Scheme 17

The reactions of zinc fluoride with acetyl protected α-D-glucosyl bromides also occurred in MeCN with β-selectivity. Crystalline zinc fluoride is only soluble in refluxing acetonitrile; therefore, the reaction of acetobromo-α-D-cellobiose **44** with ZnF_2 was performed at a high temperature[23] (Scheme 18).

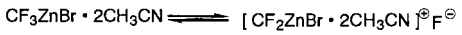


44 45

Scheme 18

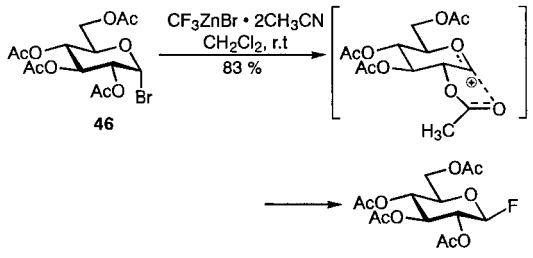
When the reaction was carried out in the presence of 2,2′-bipyridine, the yield of **45** increased to 69% without remarkable acceleration of the reaction rate (Scheme 18). The precipitation of a 2,2′-bipyridine/$ZnBr_2$ complex from the reaction mixture would reduce the concentration of the bromide ion followed by a shift of the equilibrium between bromides and fluorides.

Trifluoromethylzinc bromide is used as the fluorinating reagent of glycosyl bromides.[24] This reagent is assumed to exist in equilibrium as shown in Scheme 19.



Scheme 19

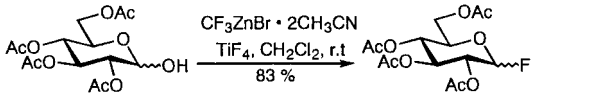
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **46** was allowed to react with this reagent to afford the corresponding fluoride **47a** in a β-selective manner (Scheme 20). This result can be explained by the presence of the oxonium ion intermediate with the assistance (anchimeric assistance) of the acetyl group in the C-2 position.



46 47a

Scheme 20

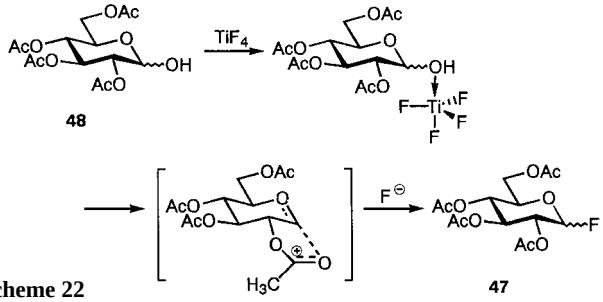
In addition, the conversion of a glycosidic OH-group into an F-group was investigated by using this reagent. Under the same conditions as described for glycosyl bromide **46**, the reaction resulted in a poor conversion. However, 2,3,4,6-tetra-*O*-acetyl-D-glucose (**48**) when treated with CF_3ZnBr•2MeCN and TiF_4 in dichloromethane gave the desired fluoride **47** in good yield (Scheme 21).



48 47

Scheme 21

In this process, TiF_4 catalyzed the formation of the oxocarbenium ion intermediate as shown in Scheme 22. However, the Lewis acid also stimulated the formation of α-glycosyl fluoride, because it retarded the anchimeric assistance of the acetyl group (Scheme 22).

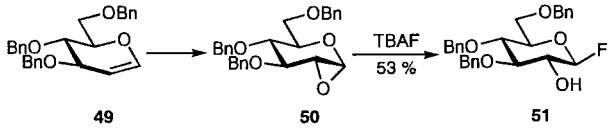


48 47

Scheme 22

2.4 Others

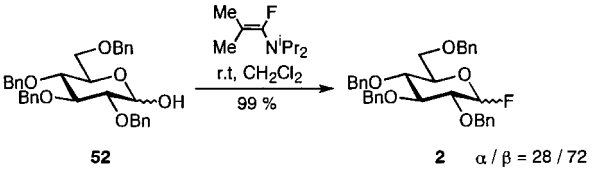
Tetrabutylammonium fluoride (TBAF) is used for the preparation of glycosyl fluorides from 1,2-anhydro- α-D-hexopyranose derivatives via the epoxidation of the glycals.[25] The perbenzylated 1,2-anhydro-α-D-hexopyranose **50** prepared by epoxidation of the corresponding glycal **49** reacted with TBAF to afford the β-glycosyl fluoride **51** in 53% yield by S_N2 pathway (Scheme 23).



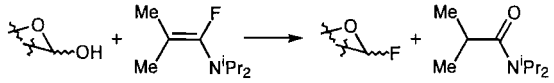
49 50 51

Scheme 23

α-Fluoroenamine was found to be an effective reagent for the conversion of various furanose and pyranose hemiacetals into the corresponding glycosyl fluoride.[26] This reagent does not affect some kinds of hydroxy-protecting groups such as benzyl, benzoyl, acetyl, acetonide, or silyl functionalities owing to the fluorination under natural conditions. By the use of this reagent, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride (**2**) could be obtained from the corresponding hemiacetal **52** with the α/β ratio = 28:72 (Scheme 24). The reaction takes place in the manner as indicated in Scheme 25, on account of the presence of an only byproduct, *N*,*N*-diisopropylisobutyramide.

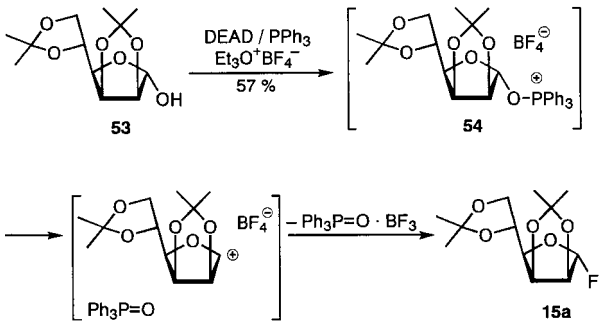


Scheme 24



Scheme 25

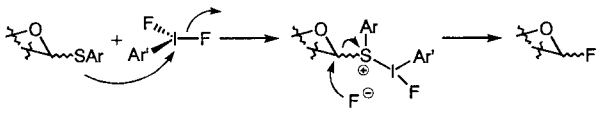
Glycosyl fluorides can also be obtained by modification of the Mitsunobu reaction[27] (Scheme 26). By exposure to triphenylphosphine, diethyl azodicarboxylate (DEAD) and triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$), diisopropylidenemannofuranose **53** was converted into the fluoride **15a**. This reaction proceeds via the unstable oxyphosphonium salt **54**, which decomposes via the stabilized carbenium ion forming the fluoride **15a**.



Scheme 26

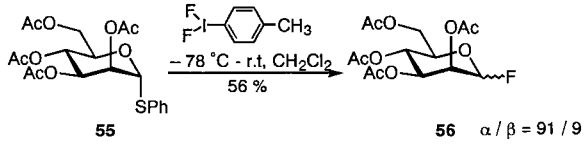
The reaction of thioglycosides with hypervalent iodoarene was reported for the preparation of the corresponding fluorides. The thioglycosides were allowed to react with 4-methyl(difluoroiodo)benzene to introduce the fluorine into the glycosyl donors via the pathway shown in Scheme 27.[28]

When the axial acetate existed at the C-2 position, an intermediate oxocarbenium ion was stabilized by the anchimeric assistance and the attack of fluoride occurred from

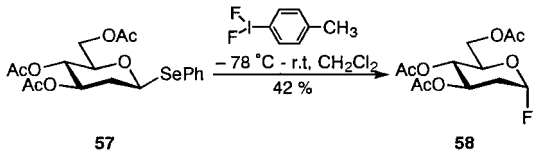


Scheme 27

the axial side (Scheme 28). However, when an α-phenylthio derivative of tetra-*O*-benzyl-D-glucose was allowed to react with the reagent, it underwent an S_N2 displacement to give the corresponding β-glycosyl fluoride. The reaction with selenoglycoside was also examined.[29] The 2-deoxyphenylselenoglycoside **57** provided the glycosyl fluoride **58** by using the same reagent via an S_N2 inversion (Scheme 29).



Scheme 28



Scheme 29

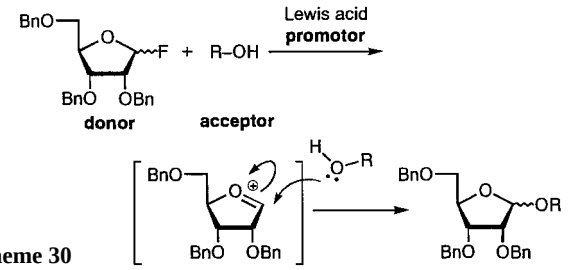
3. Reaction of Glycosyl Fluorides

Glycosyl fluorides have been known as a good sugar donor for glycosidation reactions. Therefore, they are available for C–O, C–N, and C–C bond formations under the activation of various promoters. To achieve high stereoselectivity and good yields under mild conditions, numerous studies have been carried out on the reaction of glycosyl fluorides. The following description deals with three types of bond formations according to the kind of promoter.

3.1 C–O Bond Formation

3.1.1 Lewis Acids

O-Glycosidation is composed of a glycosyl donor which is activated as an electrophile at the anomeric carbon, an alcohol as the glycosyl acceptor, and Lewis acid as the promoter. The reaction undergoes a Friedel–Crafts type pathway as represented in Scheme 30. The Lewis acid at-

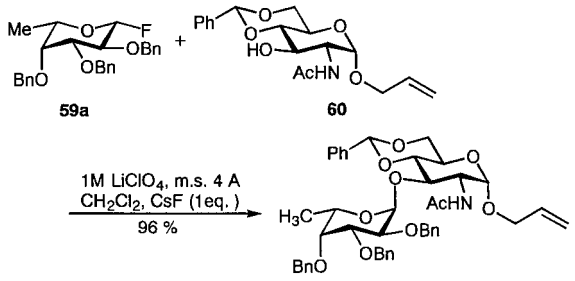


Scheme 30

tacks the fluoride to form an oxocarbenium ion, which is followed by the addition of an alcohol to give the corresponding *O*-glycoside.

Lithium Perchlorate

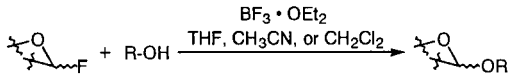
Lithium perchlorate ($LiClO_4$) is a milder Lewis acid than others used commonly, such as $SnCl_2/AgClO_4$, $BF_3 \bullet OEt_2$, and TMSOTf. Owing to its mild conditions, it is utilized for the glycosidation of acid-sensitive sugars such as fucose.[30] The disaccharide **61** of fucose was built up by the coupling of a fucose donor **59a** with an acceptor **60** in the presence of $LiClO_4$ and 1 equivalent of CsF as acid scavenger (Scheme 31).



Scheme 31

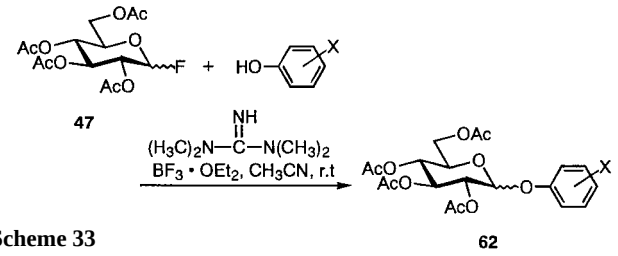
Boron Trifluoride Etherate

Since 1985, boron trifluoride etherate has been adopted as the Lewis acid in order to promote the reaction of glycosyl fluorides.[27] It catalyzes the condensation of the fluorides and the alcohols in the same manner as that of other Lewis acids (Scheme 32).



Scheme 32

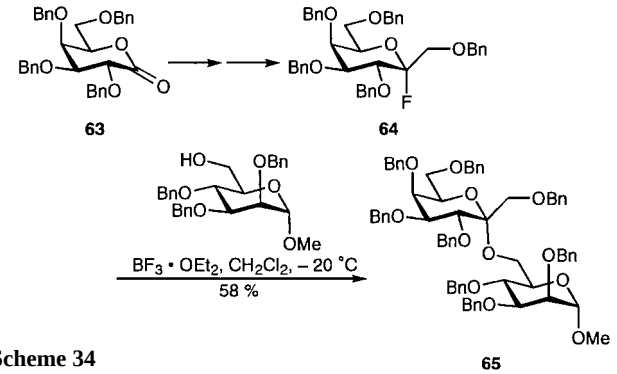
It was reported that the stereoselectivity of glycosidation of phenols in the presence of $BF_3 \bullet OEt_2$ depended on the coexistence of an amine base, 1,1,3,3,-tetramethylguanidine[31] (Scheme 33).



Scheme 33

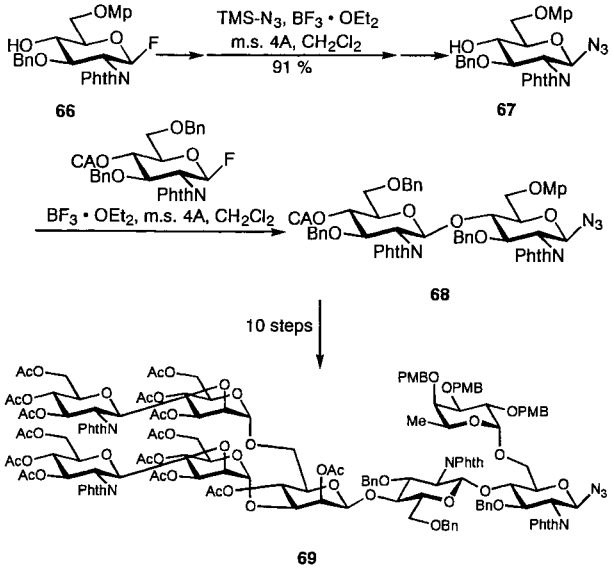
When *o*-chlorophenol (X = *o*-Cl) was used in the presence of 1,1,3,3,-tetramethyl guanidine, the desired compound **62** was formed quantitatively in the ratio of α/β = 10:90 (Scheme 33). On the other hand, in the absence of the amine base, the ratio turned to α-selectivity (α/β = 80:20, yield: 76%). As for the conditions, variations of the Lewis acid, solvents, and bases were tried, but no conditions gave better results than that mentioned above. Furthermore, the phenols with an electron-donating group exhibited high β-selectivity.

This reagent can also be applied to a variety of glycosyl substrates. The fluoride **64** derived from lactone **63** in two steps was reacted with the glycosyl acceptor in the presence of $BF_3 \bullet OEt_2$ to give the corresponding disaccharide **65** in 58% yield[32] (Scheme 34). When bis(cyclopentadienyl)zirconium dichloride/silver tetrafluoroborate was employed as the activator in place of $BF_3 \bullet OEt_2$, the reaction proceeded similarly to give **65** in 59% yield.[33]



Scheme 34

Moreover, the octasaccharide **69** was constructed from glycosyl fluorides using $BF_3 \bullet OEt_2$[34] (Scheme 35). First, the introduction of an azide group at the 1′-position was interestingly accomplished by the reaction of the fluoride **66** with trimethylsilyl azide under a catalytic amount of $BF_3 \bullet OEt_2$ in two steps. The condensation of compound **67** with the glycosyl fluoride, a derivative of **66** in the presence of $BF_3 \bullet OEt_2$ resulted in the formation of the disac-



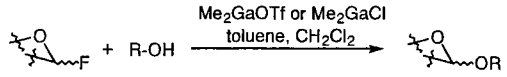
CA = chloroacetyl, Mp = p-methoxyphenyl, Phth = phthaloyl, PMB = p-methoxyphenylmethyl

Scheme 35

charide **68**. Modification of **68** in 10 steps afforded the desired octasaccharide **69** as a precursor for the core-fucosylation of *N*-glycans.

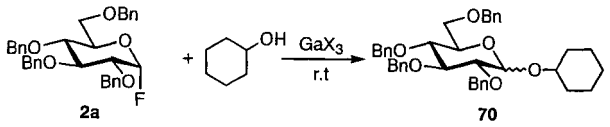
Gallium Compounds

Gallium compounds were employed as promoters for the reaction of glycosyl fluorides because of their strong affinity to fluoride.[35] The reagents were allowed to react with free alcohols to give the corresponding acetals (Scheme 36).



Scheme 36

Several kinds of Gallium reagents were prepared to examine the difference in reactivity (Scheme 37, Table 2).



Scheme 37

Table 2. Influence of Gallium Reagents in the Reaction of Fluoride **2a** with Alcohols (Scheme 37)

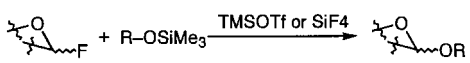
Entry	GaX_3	Solvent	Yield (%)	α/β
1	Me_2GaOTf	toluene	79	50:50
2	Me_2GaOTf[a]	toluene	88	48:52
3	Me_2GaCl	toluene	quant.	31:69
4	Me_2GaCl	CH_2Cl_2	quant.	17:83

[a] TMS ether of cyclohexanol was used as a nucleophile.

As shown in Table 2, it is obvious that the readily available Me_2GaCl is suitable for the glycosidation either in toluene, CH_2Cl_2, or MeCN. The solvent effect was observed in this reaction; the use of CH_2Cl_2 or acetonitrile resulted in relatively high β-selectivity. The reaction proceeded very slowly in acetonitrile probably because of the coordination of the lone pair electrons of the solvent to the gallium atom. When silylated alcohol was used instead of free alcohol, the reaction proceeded rapidly, but no difference was observed in the yield and stereoselectivity.

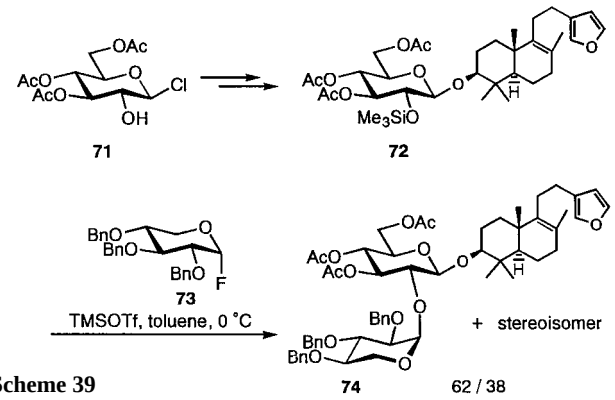
Silyl Compounds

Silyl compounds were employed in the reaction of glycosyl fluorides as a promotor by Noyori and coworkers in 1984.[36] A silyl compound such as trimethylsilyl triflate (TMSOTf) promotes the condensation of the silyl ether and the glycosyl fluoride (Scheme 38). Even if the reagent is weakly toxic, it is suitable for a large-scale reaction.



Scheme 38

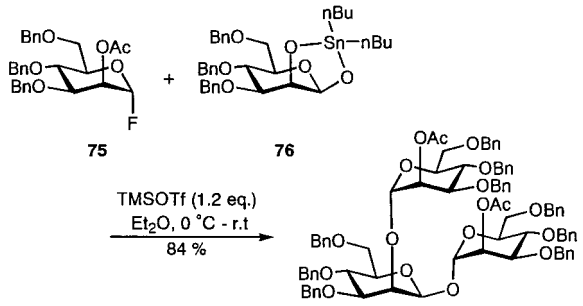
The protected diterpene glycoside, baiyunoside (**74**) was synthesized from the reaction of **72** derived from 3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride (**71**) with glycosyl fluoride **73** in the presence of TMSOTf[37](Scheme 39).



Scheme 39

As for the coupling reaction of two sugars, it was expected that **74** would be formed by the reaction of glycosyl halides and unsilylated alcohol of **72** under Köenigs–Knorr conditions. However, the reaction was unsuccessful, although, the coupling of **72** and glycosyl fluoride **73** under the conditions using TMSOTf gave disaccharide **74** and its stereoisomer in a ratio of 62:38.

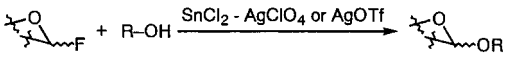
A novel approach for coupling of three sugars in one step was reported[38], namely the reaction between glycosyl fluoride and the sugar protected by a five-membered ring stannane in the presence of TMSOTf. Mannosyl fluoride **75** reacted with the stannane compound **76** to form the trisaccharide **77** stereoselectively (Scheme 40). In this method, by changing the equivalent amount of TMSOTf, the disaccharide was obtained as the major product.



Scheme 40

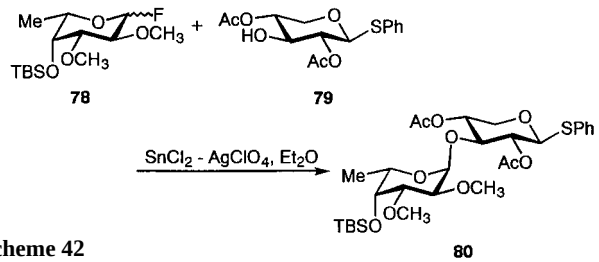
Stannous(II) Chloride

Stannous(II) chloride was used first as an activator of the glycosyl fluoride with a combination of silver salts in 1981 by Mukaiyama and coworkers for the *O*-glycosydation[39] (Scheme 41).



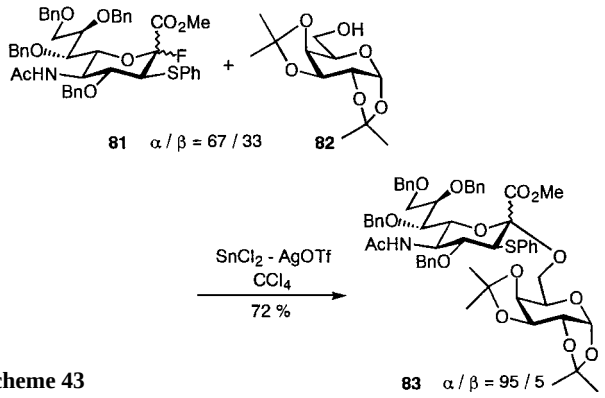
Scheme 41

The fluoride **78** derived from L-fucose was easily reacted with the acceptor glycoside **79** in the presence of $SnCl_2$/$AgClO_4$ to afford the corresponding disaccharide **80** in 57% yield with only an α-anomer[40] (Scheme 42). After deacetylation followed by methylation, the compound **80** was converted into the skeleton of polycavernoside A.



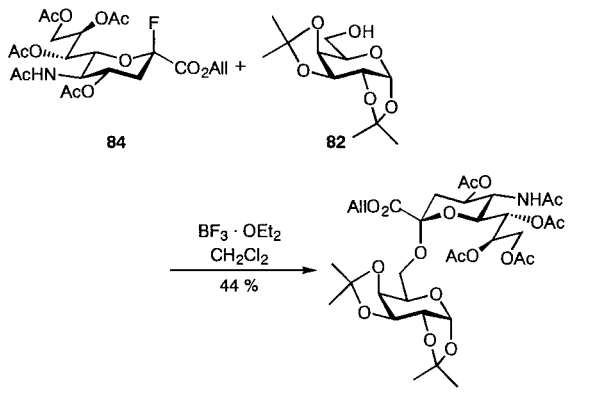
Scheme 42

The preparation of sialic acid derivatives is a difficult problem. To overcome the difficulty, the reaction of *N*-acetylneuraminic acid derivatives with glycosyl fluoride was performed in the presence of $SnCl_2$/AgOTf by Ogawa and coworkers.[41] The reaction led to the *O*-glycoside **83** with an α-isomer as the major product (Scheme 43). When Et_2O was used as solvent, the reaction proceeded with lower yield (56%) and lower stereoselectivity (α/β = 87:13).



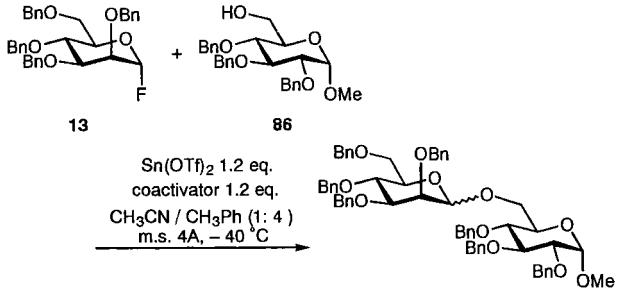
Scheme 43

Kunz and coworkers also synthesized *N*-acetylneuraminic acid derivatives by using *O*-acetylated glycosyl fluoride.[42] The fluoride **84** activated by BF_3•OEt_2 in dichloromethane reacted with the alcohol **82** to form preferentially the disaccharide **85** with the β-configuration (α/β = 17:83, Scheme 44).



Scheme 44

Usually, the stannous salt needs a coactivator such as a silver salt so that the reaction proceeds smoothly. Some researchers reported the results achieved on changing the coactivators to improve the stereoselectivity and the yield. Thus, the β-selective coupling of mannosides encountered a problem, namely that the mannoside disfavored stereoelectronically β-linkage formation, although the desired β-mannoside **87** could be synthesized as a major product from α-mannosyl fluoride **13** by changing the coactivator[43] (Scheme 45, Table 3).



Scheme 45

Table 3. Effect of Coactivator in the Preparation of **85** (Scheme 45)

Entry	Coactivator	Yield (%)	α/β
1	BF_3•OEt	80	39:61
2	$TiCl_4$	54	76:24
3	$Yb(OTf)_3$	25	40:60
4	$La(ClO_4)_3$•nH_2O	85	29:71
5	$La(ClO_4)_3$•nH_2O[a]	99	27:73

[a] 2.4 equiv of $Sn(OTf)_2$ was used.

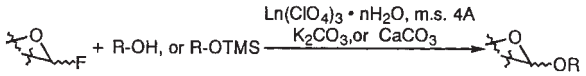
As shown in Table 3, the combination of $Sn(OTf)_2$ and $La(ClO_4)_3$•nH_2O as a coactivator was the most effective promoter for β-mannosylation. When $SnCl_2$ was employed in place of $Sn(OTf)_2$, the yield decreased to 47% with poor selectivity (α/β = 46:54).

O-Glycosidation Under $SnCl_2$/$AgClO_4$ System; General Procedure:[39]

To a mixture of stannous chloride (0.2 mmol), silver perchlorate (0.2 mmol), and molecular sieves 4A was added an ether solution (4 ml) of the alcohol (0.17 mmol) and the glycosyl fluoride (0.2 mmol) at –15 °C and the reaction mixture was stirred at the same temperature for 24 h. After filtration, the filtrate was washed with aqueous sodium bicarbonate, dried over Na_2SO_4 and evaporated. The purification of the residue by TLC (silica gel) gave the desired compound.

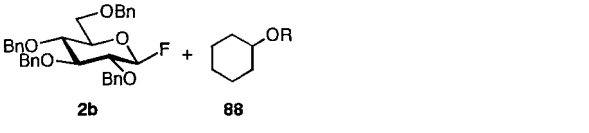
Rare Earth Metal Salts

Recently, rare earth metal salts were reported as Lewis acids to promote the reaction of glycosyl fluorides due to the large dissociation energies of rare earth metals–fluorine.[44] (Scheme 46)



Scheme 46

To investigate their characteristics, various kinds of rare earth metal salts were used[45,46] The reaction of the fluoride **2b** with silylated or free alcohol **88** revealed their reactivity and stereoselectivity (Scheme 47, Table 4). It is noteworthy that the glycosidation did not proceed in the presence of $Gd(ClO_4)_3•nH_2O$, $Ho(ClO_4)_3•nH_2O$, $Yb(ClO_4)_3•nH_2O$, and $Y(ClO_4)_3•nH_2O$. This fact suggests that the rare earth perchlorates with a certain range of ionic radii can act as effective activators. When silylated or free alcohol was examined for the glycosidation, the silylated alcohol proved more favourable. Furthermore, when Et_2O was used instead of MeCN as a solvent, the glycosidation was turned to α-selectivity.



Scheme 47

Table 4. Influence of Rare Earth Metal Salts in the Reaction of **2b** with **88** (Scheme 47)

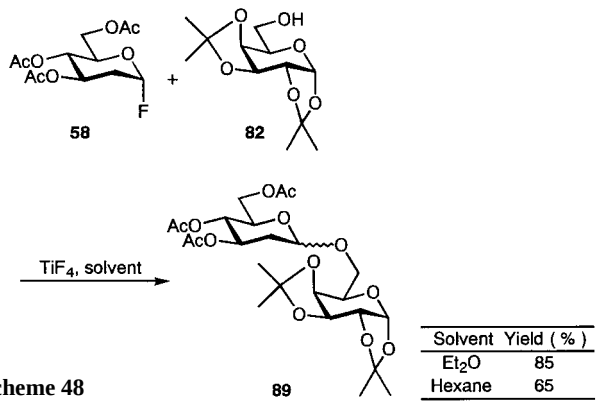
Entry	$Ln(ClO_4)_3•nH_2O$	R	Solvent	Yield (%)	α/β
1	$La(ClO_4)_3•nH_2O$	TMS	MeCN	82	8:92
2	$Ce(ClO_4)_3•nH_2O$	TMS	MeCN	89	β
3	$Pr(ClO_4)_3•nH_2O$	TMS	MeCN	80	β
4	$Eu(ClO_4)_3•nH_2O$	TMS	MeCN	61	15:85
5	$Yb(OTf)_3$	H	MeCN	63	6:94
6	$La(OTf)_3$	H	MeCN	36	β
7	$La(ClO_4)_3•nH_2O$	TMS	Et_2O	94	α

***O*-Glycosidation with Rare Earth Metal Salts; General Procedure:**[46] An activator (a rare earth metal salt, 1.2 equiv to a glycosyl donor), and an inorganic base (4.0 equiv of K_2CO_3 or $CaCO_3$) and molecular sieves 4Å were dried at ca. 110 °C under vacuum for 2 h. A solution (1 mL) of glycosyl fluoride (0.055 mmol) and glycosyl acceptor (1.2 equiv) was then added. After the reaction was complete, sat. aq $NaHCO_3$ solution was added and filtered. The usual workup with the filtrate gave a product which was purified by silica gel column chromatography.

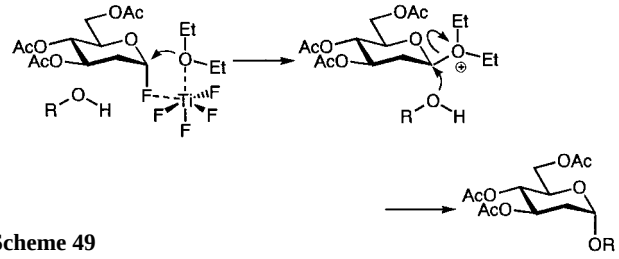
Titanium Tetrafluoride

The stereoselective coupling of 2-deoxy glycosyl fluoride was carried out with use of TiF_4 as a catalyst in 1986.[47] When the glycosyl fluoride **58** was allowed to react with sugar **82** in the presence of TiF_4 in Et_2O, the reaction proceeded in an α-selective manner (α/β = 83:17). However, when the reaction was performed in hexane, a β-isomer of the disaccharide **89** was obtained as the major product (α/β = 40:60)[48] (Scheme 48).

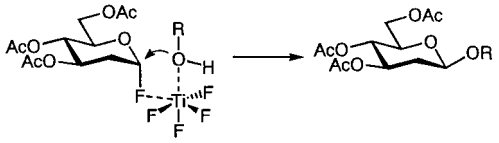
These facts can be explained by the coordination of the solvent or nucleophile to TiF_4 as shown in Schemes 49 and 50. With Et_2O as a solvent, the reaction starts with the



Scheme 48



Scheme 49

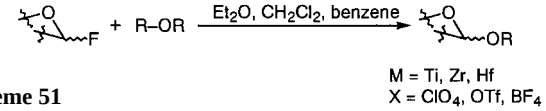


Scheme 50

attack of Et_2O coordinated with TiF_4 in an S_N2-like manner followed by a second attack of the nucleophile from the α-face. In the case of hexane, the nucleophile attacks the anomeric carbon as coordinated only by TiF_4 in an S_N2 mechanism to give rise to the β-isomer.

Bis(cyclopentadienyl)metal Derivatives

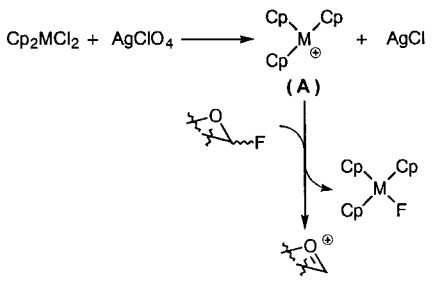
Group IV_B metallocenes (Cp_2MCl_2 ; M = Ti, Zr, Hf) were presented by Suzuki and coworkers as a mild activator of glycosyl fluorides in 1988.[16, 17] The reagent itself is inert as an activator. Nevertheless, the addition of an equimolar amount of $AgClO_4$ proceeds the reaction smoothly (Scheme 51). The activation mechanism can be explained by the cationic complex (**A**) which may act as a highly fluorophilic species as illustrated in Scheme 52.



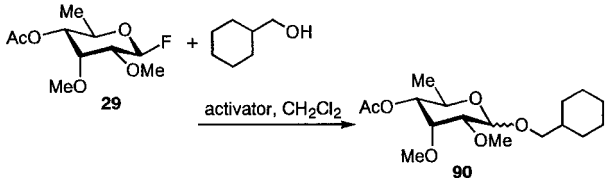
Scheme 51

Their reactivities were examined by using cyclohexylmethanol as the model compound (Scheme 53).

The rough order of their reactivities was found to be Zr = Hf > Ti. The stereoselectivity of the Zr-system relied on



Scheme 52

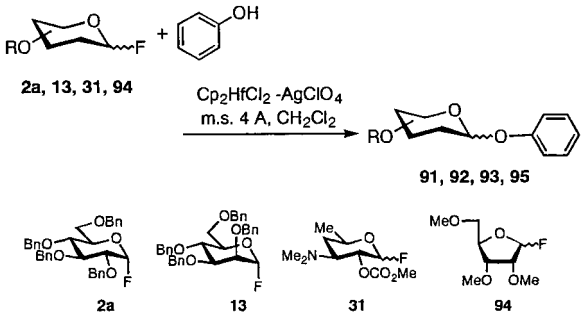


Entry	Activator	Yield (%)	α / β
1	Cp_2TiCl_2 - $AgClO_4$	90	36 / 64
2	Cp_2ZrCl_2 - $AgClO_4$	90	55 / 45
3	Cp_2HfCl_2 - $AgClO_4$	86	63 / 37

Scheme 53

the solvent. For example, Et_2O showed α-selectivity and benzene showed β-selectivity as described for titanium tetrafluoride.

Indeed, this reagent can be applied to various sugars. The combination of $Cp_2HfCl_2/AgClO_4$ was allowed to react with four types of sugars[49] (Scheme 54, Table 5).



Scheme 54

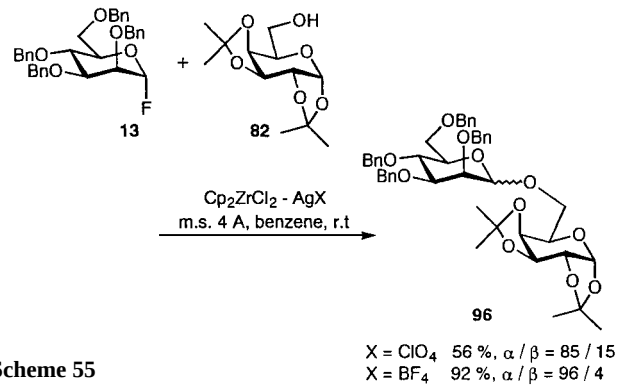
Table 5. Compounds **91–93, 95** Prepared

Entry	Fluoride	Temp (°C)	Product	Yield (%)	α/β
1	**2a**	–78 to –30	**91**	82	48:52
2	**13**	–78 to –20	**92**	90	α
3	**31**	0 to r.t.	**93**	93	69:3l
4	**94**	–78	**95**	74[a]	24:76

[a] 5% of *C*-glycoside was isolated.

As for the perbenzylated fluorides **2a** and **13**, the reaction proceeded cleanly at –30 °C with high yield. In addition, a characteristic of this reagent that the anomeric activation was not interrupted by the basic amino group was revealed in this study (Entry 3, Table 5). With use of pentose **94**, the reaction gave rise to the desired *O*-glycoside **95** together with 5% of *C*-glycoside, 2-(2,3,5-tri-*O*-methyl-D-ribofuranosyl)phenol.

To achieve α-selective glycosidation of perbenzylated D-mannosyl fluoride, the coactivator of Cp_2ZrCl was improved.[50] The system of $Cp_2ZrCl/AgBF_4$ was found to be more effective in benzene as the most preferable solvent. The reaction of the fluoride **13** with the alcohol **82** was examined in the presence of $AgBF_4$ or $AgClO_4$ as a common coactivator (Scheme 55). Compared with $AgClO_4$, $AgBF_4$ increased the yield of **96** from 56% to 92% and the α-selectivity to α/β = 96:4.

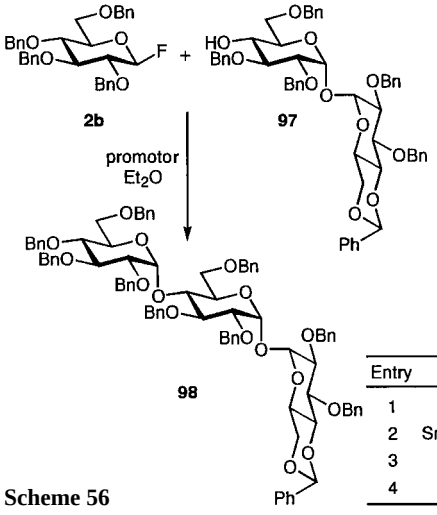


Scheme 55

$Cp_2MCl_2/AgClO_4$-Promoted Glycosidation; General Procedure:[16]
To a mixture of glycosyl fluoride (0.0542 mmol), alcohol (2 equiv) and powdered molecular sieves (4Å) in CH_2Cl_2 (2.5 mL) was added Cp_2MCl_2 (5 equiv) followed by $AgClO_4$ (5 equiv). After the addition of sat. aq $NaHCO_3$ solution and filtration through a Celite pad, the mixture was extractively worked up. Purification by TLC (eluent, hexane/Et_2O = 1:1) gave the corresponding glycoside.

3.1.2 Triflic Anhydride

Among the Lewis acids used for the glycosidation of glycosyl fluorides, triflates are indispensable. Therefore, some triflates were examined to compare their reactivities for the glycosidation with an unreactive glycosyl acceptor.[51] As shown in Scheme 56, trimethylsilyl triflate, stan-



Entry	Promotor	Yield (%)
1	TMSOTf	45
2	$SnCl_2$ / AgOTf	65
3	TiF_4	68
4	TfOTf	92

Scheme 56

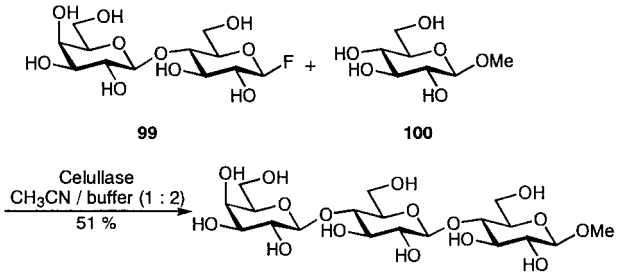
nous chloride / silver triflate, and titanium tetrafluoride were compared in synthesis of trisaccharide **98** under similar conditions. The reaction occurred in a Königs–Knorr manner to suggest the relative reactivity (TMSOTf < $SnCl_2/AgClO_4 \leq Tif_4$ < TfOTf).

3.1.3 Enzymes

Cellulase

Many efforts have been dedicated to the stereoselective preparation of cellulose having a β-(1 → 4) glycosidic linkage. In the 1990s a novel method for synthesis of oligosaccharide using cellulase was devised, From several studies, the most suitable conditions were determined by changing the solvents, enzymes, and concentration.[52–55]

By exposure to cellulase (from *Trichoderma viride*), elongation of the disaccharide **99** was carried out with complete stereoselectivity (Scheme 57). As the starting material, the disaccharide **99** was chosen because the smallest subunit recognized by the enzyme may be a disaccharide. In addition, the β-fluoride **99** was employed as the starting material in order to form a β-(1 → 4) linkage via a "double displacement mechanism" on the active site of the enzyme as shown in Figure 1. With respect to the monosaccharide acceptor, sugars with an axial group at the 1 or 3 position were not suitable for this method, because the axial group prevents the binding to the enzyme.



99 + **100** → **101**

Scheme 57

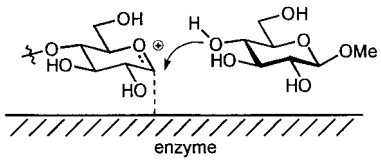
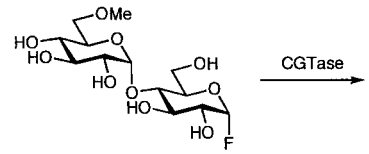


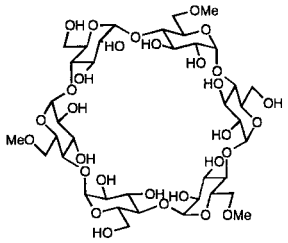
Figure 1. Double Displacement Mechanism on the Active Site of the Enzyme.

Cyclodextrin Glucosyltransferase (CGTase)

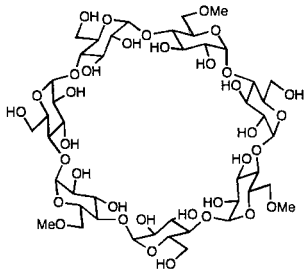
Glycosyl fluoride can also be a good substrate for cyclodextrin glycosyltransferase (CGTase).[56] The reaction starts with incubation of the glycosyl fluoride and CGTase for 20 hours. By treatment with enzyme, 6′-*O*-methylmaltosyl fluoride (**102**) could be converted into α-cyclodextrin (**103**) in 42 % yield together with β-cyclodextrin (**104**) and γ-cyclodextrin (**105**) in 16 and 13% yields, respectively (Scheme 58).



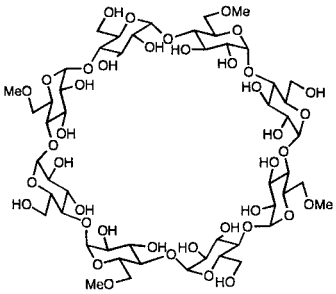
102



103 +



104 +

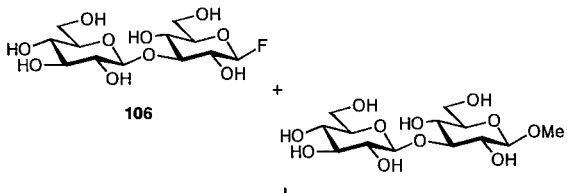


105

Scheme 58

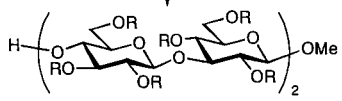
1,3-1,4-β-Glucanase

Enzymatic synthesis of β-D-glucooligosaccharide was reported in 1997 by reacting glycosyl fluoride with 1,3-1,4-β-glucanase.[57] In maleate buffer/MeCN (2:3), the reaction of β-laminaribiosyl fluoride (**106**) with methyl glycoside (**107**) occurred to afford tetrasaccharide **108**. Next, the reaction mixture was fully acetylated and purification gave the compound **109** in 46% yield. Treatment of **109** with



106 + **107**

β-1,3-1,4-glucanase

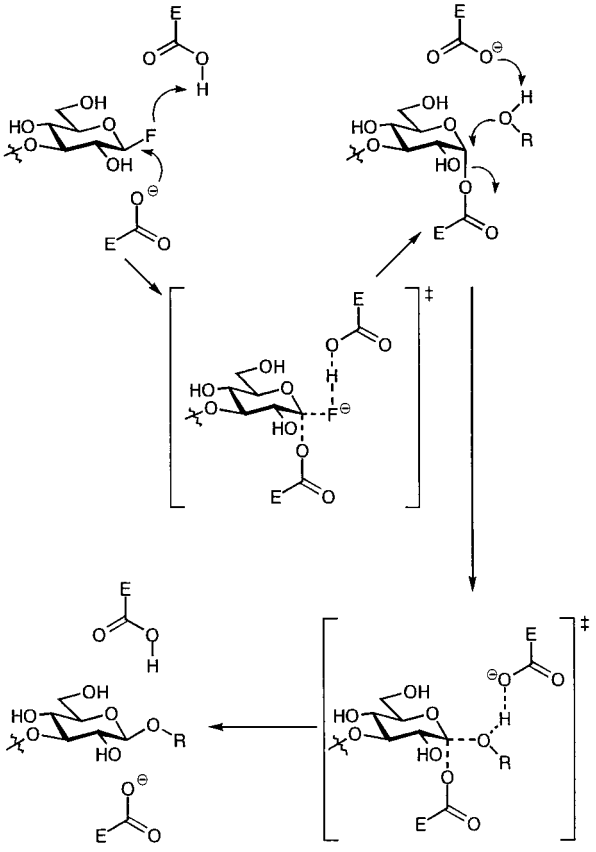


108 R = H
109 R = Ac

Scheme 59

MeONa in MeOH provided the free methyl tetrasaccharide **108** in 40% overall yield (Scheme 59).

The reaction mechanism is presented in Scheme 60. Glycosidation takes place on the free β-face followed by elimination of enzyme.



Scheme 60

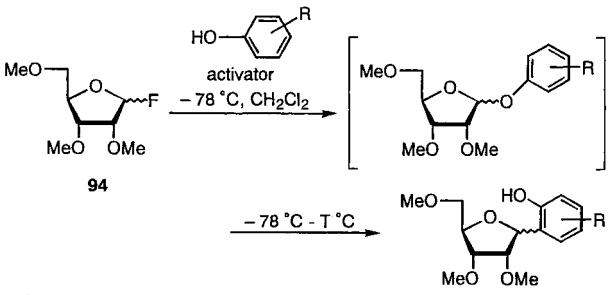
3.2 C–C Bond Formation

Recently, C–C bond formation of glycosides, the so-called *C*-glycosidation, has attracted much attention among chemists and biologists. Since *C*-glycosides such as showdomycin have been isolated from nature and showed biological activities as an antitumor and antivirus agent, a highly stereoselective and efficient method for the synthesis of *C*-glycoside has been strongly desired.

3.2.1 Lewis acids

In the same manner as C–O bond formation with Lewis acids, *C*-glycosidation can proceed with Lewis acids. It was observed that *C*-glycosidation took place via the rearrangement of *O*-glycoside under Lewis acids.[58] The two-step process is as follows: The *O*-glycosidation proceeded rapidly at –78 °C within 10 minutes in standard operation and, after the formation of *O*-glycoside, gradual warming results in the formation of *C*-glycoside via rearrangement.

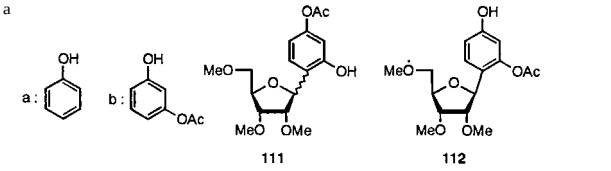
As shown in Scheme 61 (Table 6), it is evident that BF_3•OEt_2 is totally ineffective and that $Cp_2HfCl_2/AgClO_4$



Scheme 61

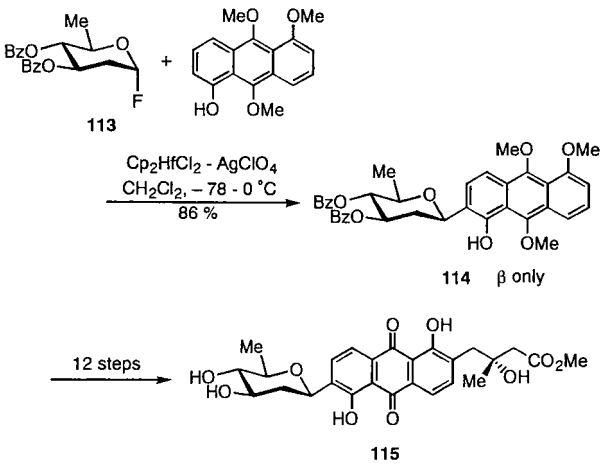
Table 6. Compounds **110–112** Prepared[a]

Entry	Fluoride	Acceptor	Activator	Temp (°C) (–78 to T)	Product	Yield (%) (α/β)
1	**94**	a	BF_3•OEt_2	– 5	**110**	45 (83:17)
2	(α/β = 50/50)		$SnCl_2$	–10	**110**	51 (80:20)
3	Ref. 58		Cp_2HfCl_2/ $AgClO_4$	–20	**110**	71 (7:93)
4	**94** (β)	b	BF_3•OEt_2	–10	**111** **112**	81 (6:94) 11 (β)
5	Ref. 59		Cp_2HfCl_2/ $AgClO_4$	–10	**111** **112**	83 (6:94) 8 (β)



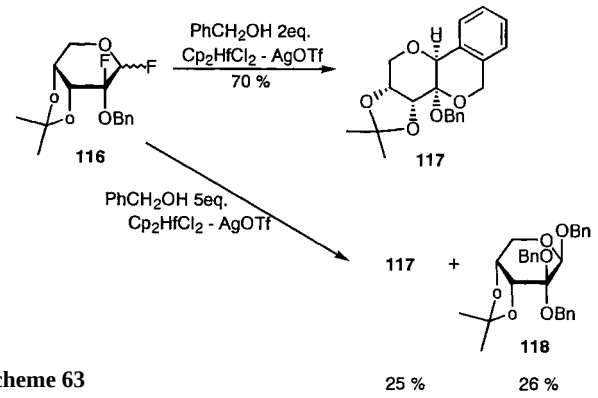
is suited for this reaction rather than $SnCl_2$. The reaction with $Cp_2HfCl_2/AgClO_4$ gave exclusively β-*C*-glycoside as the major product. In Entries 4 and 5, the formation of a small amount of regioisomer **112** by the direct Friedel–Crafts type coupling (not via the rearrangement) is noted.

As an extension of this study, total synthesis of Vineomycine B_2 methyl ester (**115**) was performed using this method.[60] In the step of *C*-glycosidation, $Cp_2HfCl_2/AgClO_4$ was employed with reference to the results in Table 6 (Scheme 62).



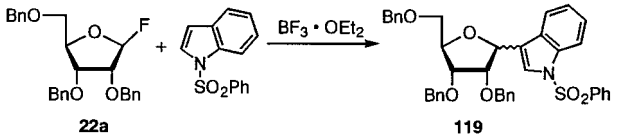
Scheme 62

When 1,2-difluorocarbohydrate was used as the sugar donor, both *O*-glycosidation and *C*-glycosidation occurred at the same time under specific conditions.[61] The products depended on the equivalent of the used alcohol (Scheme 63). By treatment with 2 equivalents of benzyl alcohol, the isochroman derivative **117** was derived from difluorosugar **116** in 70% yield. However, with 5 equivalents of alcohol, tribenzyl compound **118** was obtained in 26% yield together with the cyclic compound **117** (25%). From these results, it is implied that an oxocarbenium ion is produced when the OBn group attaches to the carbon at position 2. Furthermore, tribenzyl product **118** was obtained as the only product by reaction with 10 equivalents of $PhCH_2OH$.



Scheme 63

Further, the stereocontrolled glycosidation reaction was demonstrated by changing solvents and temperature in the presence of BF_3•OEt_2.[62] The reaction of 2,3,5-tri-*O*-benzylribofuranosyl fluoride (**22a**) with *N*-phenylsulfonylindole in CH_2Cl_2 led to the corresponding *C*-nucleoside **119** with β-selectivity (Scheme 64, Table 7).



Scheme 64

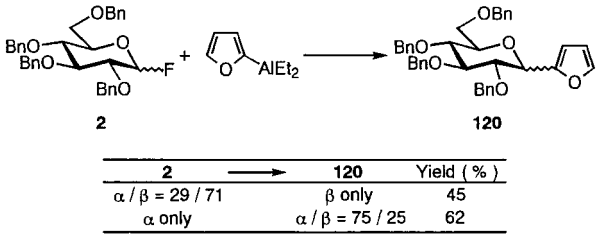
Table 7. Effect of Solvent on the Preparation of **119** (Scheme 64)

Entry	Solvent	Temp (°C)	Yield (%)	α/β
1	CH_2Cl_2	–15	96	11:89
2	EtCN	0	23	80:20
3	CH_2Cl_2/EtCN (2.5%)	–78	72	91:9
4	Et_2NO_2	–78	74	86:14
5	Et_2NO_2	–60	96	71:29
6	Et_2NO_2	–50	93	41:59
7	Et_2NO_2	–40	99	9:91
8	Et_2NO_2	–15	94	9:91

In contrast to CH_2Cl_2, the α-isomer of **119** was predominantly obtained with EtCN as a solvent. This result is probably attributed to its affinity to the oxocarbenium ion formed as an intermediate in this reaction. To improve the yield in EtCN, the use of CH_2Cl_2/EtCN (Entry 3, Table 7) resulted in α-selectivity with good yield. As a general tendency of the reaction temperature, a high temperature gave the β-isomer while a low temperature gave the α-isomer. The relation between temperature and stereoselectivity was investigated in detail with use of $EtNO_2$. When the reaction was performed at –78 °C, the ratio of α/β was 86:14. However, with warming up, the ratio turned to 9:91 which showed an equilibrium value at –15 °C.

3.2.2 Metal Reagents

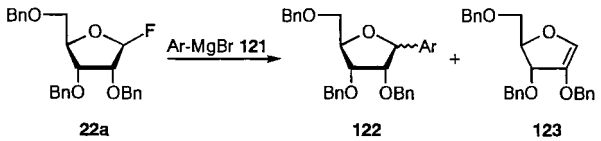
The reactions between glycosyl fluoride and metal reagents without Lewis acids were reported. The aluminated furan was allowed to react with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride **2** to give the corresponding *C*-glycoside **120** in moderate yield[63] (Scheme 65).



Scheme 65

The reaction of the fluoride **2** and the aluminated furan proceeded β-dominantly with the ratio of α/β = 29:71, while the α-isomer of **2** gave the product **120** with α/β = 75:25. Judging from these results, it can be said that the oxocarbenium ion is not an intermediate in this reaction.

Grignard reagents can also react with glycosyl fluorides easily without activators to afford *C*-glycosides[64] (Scheme 66, Table 8). First, the reaction of β-fluoride **22a** with 2-thienylmagnesium bromide (**121a**) was achieved to yield β- *C*-nucleoside **122a**, predominantly. Since the same result was observed for both α- and β- fluorides, the anomeric configuration of **22** was not important in this reaction. This result implies that the reaction proceeds via the oxocarbenium ion as an intermediate. On the other hand, cadmium and zinc salts of thiophene did not exhibit better results. In addition, the reaction did not proceed in the presence of a Lewis acid.

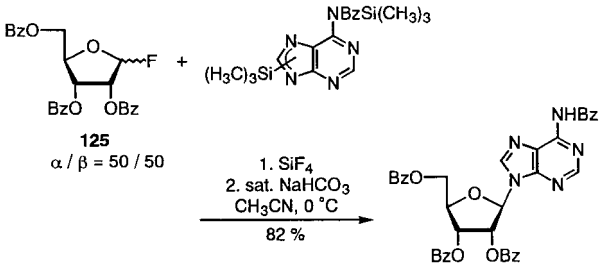


Scheme 66

Next, the introduction of benzene derivatives was examined. In contrast to thiophene, Grignard reagents of benzene derivatives gave the expected *C*-glycosides **122** together with glycal **123** as shown in Table 8. It is noted

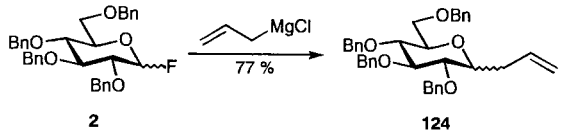
Table 8. Compounds **122, 123** Prepared

Entry	Ar in **121**	Temp (°C)	Yield (%)		α:β
			122	**123**	
1	2-thiophenyl	r.t.	65	0	8/92
2	Ph	50	57	29	β
3	4-ClC_6H_4	50	67	0	β
4	4-$MeOC_6H_4$	50	45	51	β
5	1-naphthyl	50	54	0	β



Scheme 68

that the yield of the glycal was increased along with the benzene derivatives bearing a strong electron-donating group. Furthermore, the benzyl-protected glycosyl fluoride **2** was allowed to react with allyl magnesium chloride to afford the *C*-glycoside **124** (α / β = 35 / 65) in 77% yield (Scheme 67).



Scheme 67

Coupling of Glycosyl Fluoride with Grignard Reagents; General Procedure:[64]
To a solution of glycosyl fluoride (0.15 mmol) in THF (2 mL) was added freshly prepared Grignard reagent (5 equiv) and the resulting mixture was warmed up to 50 °C. After the reaction was complete, H_2O was added and the mixture extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4)and evaporated. Purification (2 times) by preparative TLC (eluent; toluene/EtOAc, 40:1) afforded the desired *C*-glycoside.

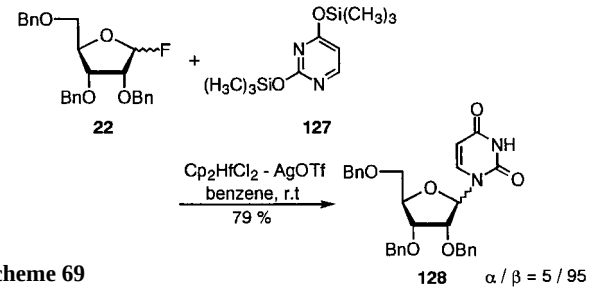
3.3 C–N, C–S Bond Formation

C–N bond formation has been performed widely by use of glycosyl fluorides, because the nucleosides in DNA are composed of a C–N bond between the sugar and base moieties. *S*-Glycosylation as well as *N*-glycosylation has been utilized with glycosyl fluorides as sugar donors in total synthesis of natural products.

3.3.1 Lewis Acids

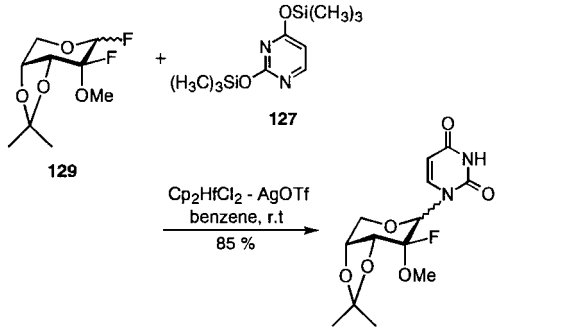
Most C–N and C–S bond formations can be accomplished in the presence of Lewis acids. A silylated adenine derivative was introduced to the glycosyl fluoride **125** by treatment of a catalytic amount of SiF_4 in good yield[65] (Scheme 68). When other Lewis acids were employed in place of SiF_4, larger amounts of the activators were required to obtain high yields.

Metallocene derivatives (Cp_2MCl_2/AgX; M = Hf, Zr, X = ClO_4, OTf) could promote C–N bond formation of glycosyl fluorides.[66, 67] When the benzyl-protected ribosyl fluoride was allowed to react with silylated uracil by the activation of Cp_2HfCl_2/AgOTf, the β-*N*-nucleoside **128** was formed predominantly in 79% yield (Scheme 69). Compared with Cp_2HfCl_2, Cp_2ZrCl_2 was less reactive in this reaction. The reaction proceeds via an oxocarbenium ion as an intermediate, since the same result was also obtained by use of the α-isomer of the starting material. In addition, with Ac or Bz groups in place of a Bn group as *O*-protection, the fluoride **22** was inert against uracil derivative **127**.



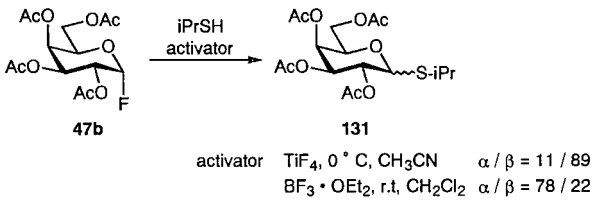
Scheme 69

In further investigation, silylated uracil **127** was introduced to the vicinal difluorocompound **129** under the same conditions. The coupling led to *N*-glycoside **130** in 85% yield with the ratio of α/β = 87:13 (Scheme 70).



Scheme 70

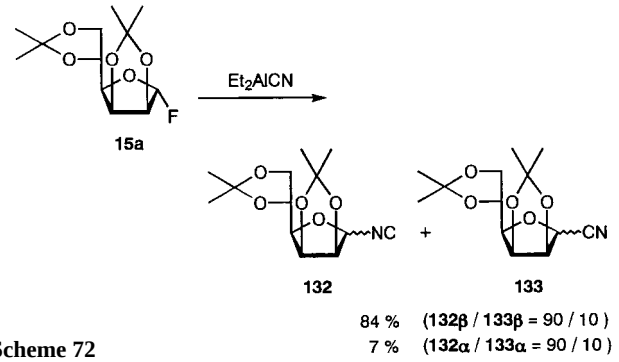
Moreover, a stereocontrolled thioglycosidation was carried out by changing the Lewis acid.[68] When TiF_4 was employed, the reaction proceeded with β-selectively at 0 °C in MeCN. On the other hand, the use of BF_3•OEt_2 as an activator changed the reaction into an α-dominant manner (Scheme 71).



Scheme 71

3.3.2 Metal Reagents

Glycosyl isocyanide can be converted into a wide variety of derivatives. Many studies have been devoted to form the glycosyl isocyanide. Using an aluminum reagent, the synthesis of glycosyl isocyanide was achieved.[69] By exposure to diethylaluminum cyanide, mannosyl fluoride **15a** was converted into the corresponding glycosyl isocyanide **132** along with the byproduct, *C*-glycosyl cyanide **133** (Scheme 72).



Scheme 72

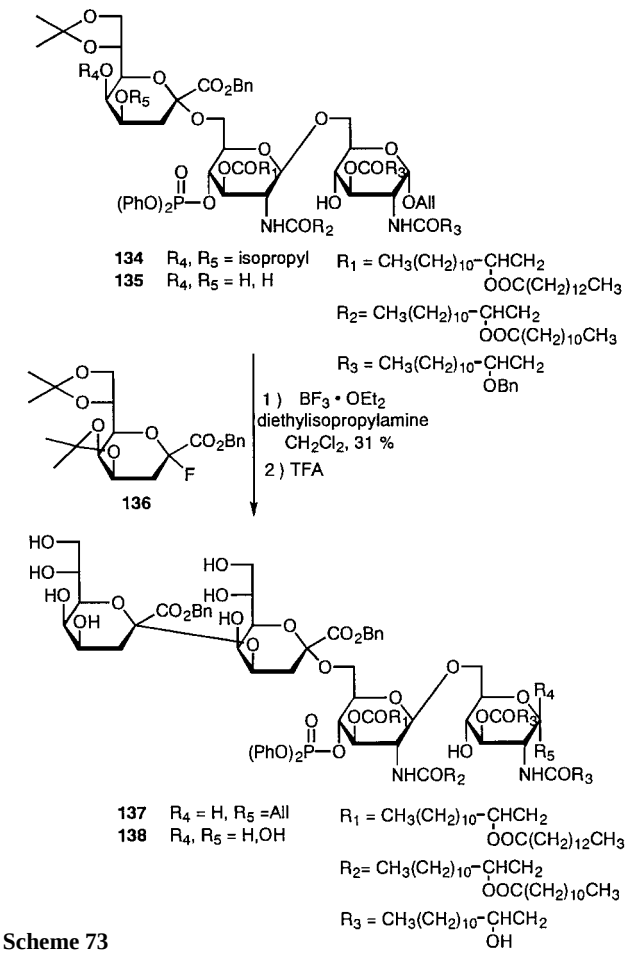
4. Total Synthesis of Natural Products

Glycosyl fluorides are versatile sugar donors on account of their stability and ease of handling compared with other sugar halides. Consequently, they have been utilized for the total synthesis of natural products. In total synthesis, most sugar fluorides are allowed to react with acceptors in the presence of Lewis acids such as Cp_2MCl_2/AgX (M = Hf, Zr; X = ClO_4, OTf), $SnCl_2/AgX$ (X = ClO_4, OTf), and BF_3•OEt_2.

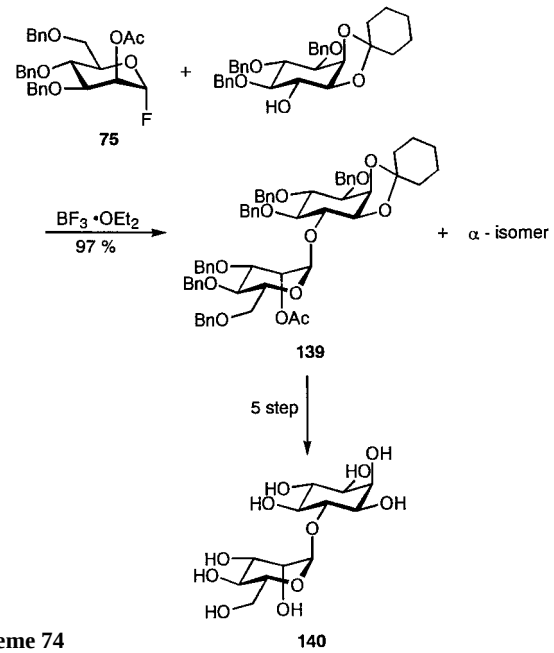
4.1 BF3•OEt2

Lipopolysaccharide (LPS) derivative was constructed from a trisaccharide intermediate **134**.[70] After deprotection of **134**, alcohol **135** was connected to the glycosyl fluoride **136** in the presence of BF_3•OEt_2 to give the tetrasaccharide **137**, ready for deprotection to convert into the expected LPS derivative **138** (Scheme 73).

Further, the synthetic method of D-*myo*-inositol monomannnoside was reported using BF3•OEt_2 as a catalyst.[71] The glycosidation of glycosyl fluoride **75** with a protected inositol acceptor was carried out in the presence of BF_3•OEt_2 to give diastereoisomers of **139** in 97% yield, which were then deprotected and separated by chromatography. The following 5-step treatment provided the D-*myo*-inositol monomannnoside **140** (Scheme 74).



Scheme 73

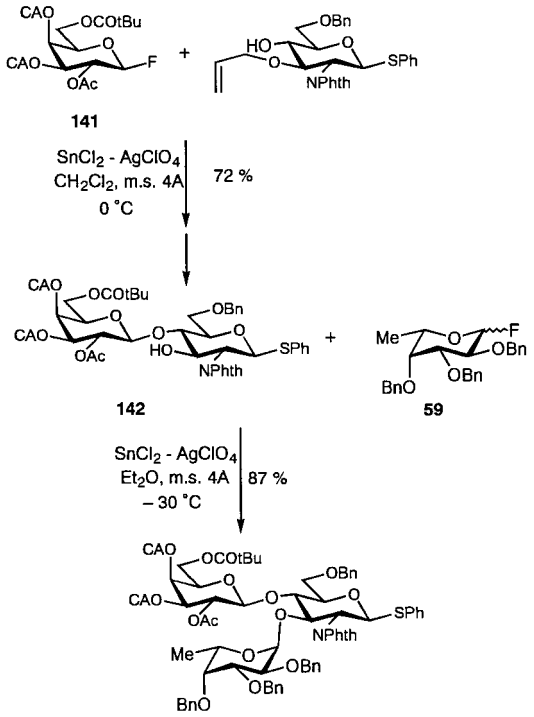


Scheme 74

4.2 $SnCl_2/AgX$ (X = ClO_4, OTf)

Sialyl Lewis X antigenic determinant (SLe^X) has drawn wide attention and many studies have been carried out on the total synthesis of SLe^X. Nicolaou and coworkers re-

ported the total synthesis of trimeric Le^X in 1990.[72] Here, only the construction of the basic framework is introduced (Scheme 75). The coupling of galactosyl fluoride **141** with the sugar acceptor as shown in Scheme 75 under $SnCl_2/AgClO_4$ system gave stereospecifically the corresponding β-glycoside, which was deprotected to be disaccharide **142**. Further glycosidation took place with the glycosyl fluoride **59** to give the basic skeleton **143**, from which the expected trimeric Le^X was synthesized.

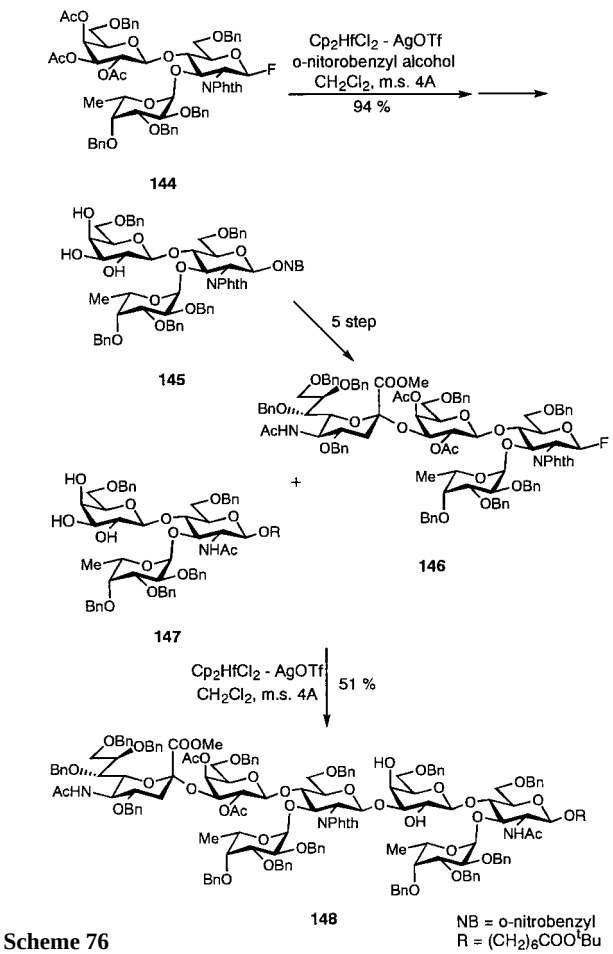


Scheme 75

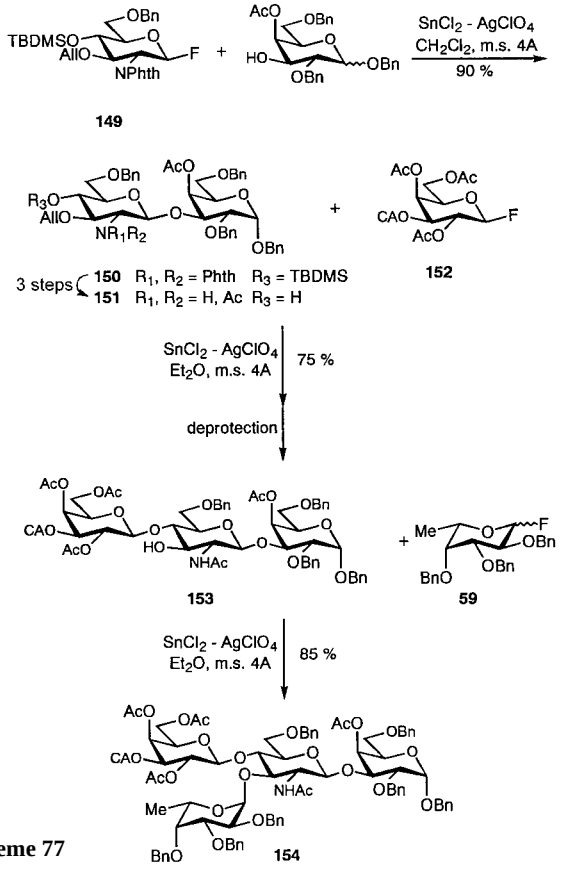
In addition, sialyl dimeric Le^X was synthesized from **144** using $Cp_2HfCl_2/AgOTf$ system[73] (Scheme 76). The fluoride **144** was converted into trihydroxy compound **145**. The 5-step dimerization of the Le^X skeleton was carried out with use of $Cp_2HfCl_2/AgOTf$ as a catalyst to give the compound **146**. Similarly, the fluoride **146** was allowed to react with **147** to give **148** in 51% yield.

As an extension of this study, the synthetic strategy of the framework was improved.[74] The fluoride **149** derived from D-glucosamine was allowed to react with a glycosyl acceptor in the presence of $SnCl_2/AgClO_4$ to form stereospecifically β-linked glycoside **150**, which was then deprotected to give the compound **151**. The glycosidation reactions with the fluoride **152** and **151** gave **153**, which was converted to Le^X framework **154** by coupling with **59** (Scheme 77).

On the other hand, Danishefsky and his coworkers applied the glycals for the total synthesis of SLex.[75] The coupling of tri-*O*-benzyl fucosyl fluoride **59** with glycal **155** using $SnCl_2/AgClO_4$ as an activator provide disaccharide **156** in 50 % yield together with 40 % of two isomers. Two glycosidations on the disaccharide **156** led to the formation of

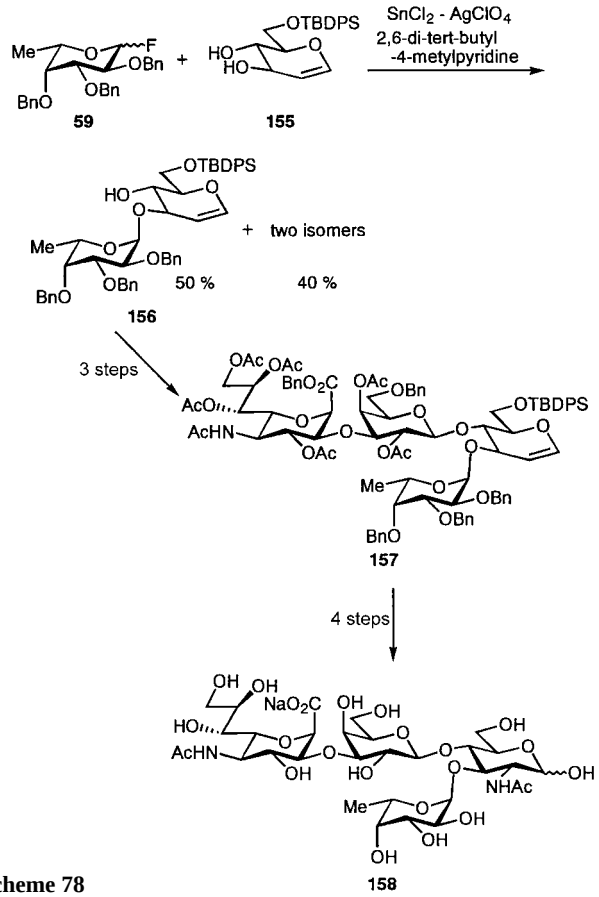


Scheme 76



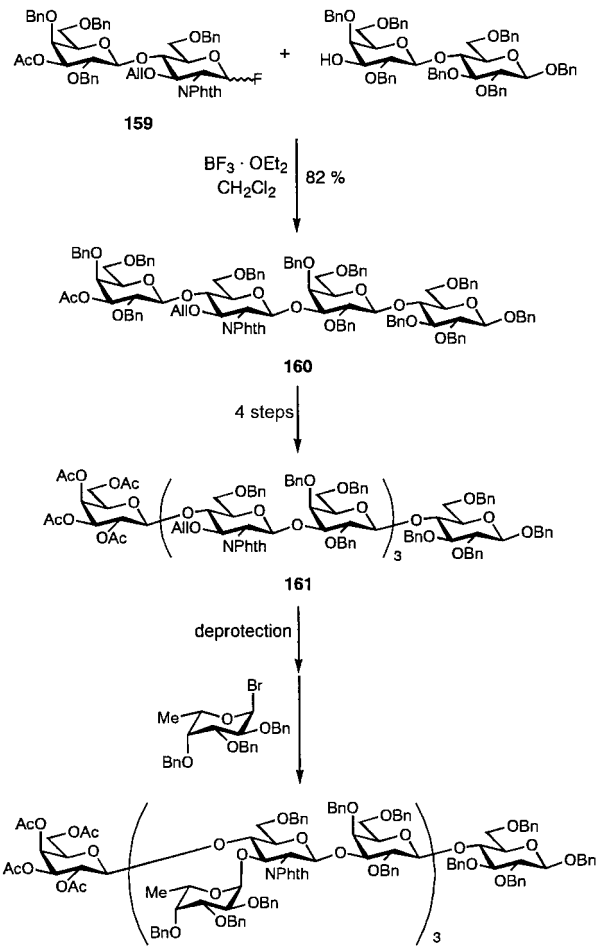
Scheme 77

a key intermediate, tetrasaccharide glycal **157**. After 4 steps of treatments, SLe^X **158** was entirely synthesized (Scheme 78).



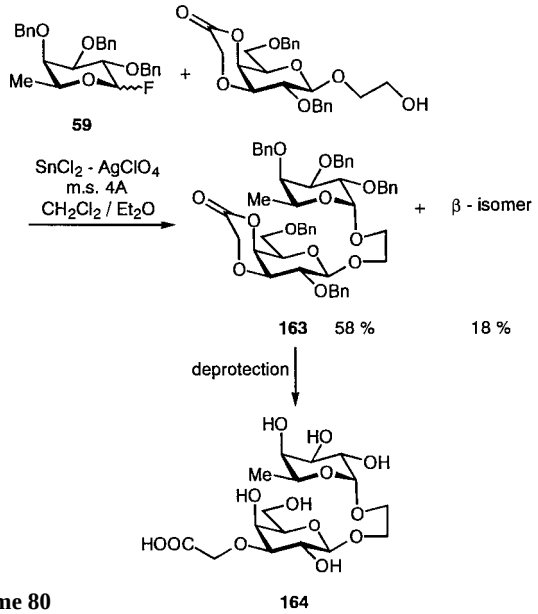
Scheme 78

Moreover, Kunz and coworkers reported the total synthesis of trimeric Le^X.[76] They synthesized oligosaccharide chain at first using repeated chain extension with glycosyl fluorides (Scheme 79). Subsequent introduction of the α-fucoside branchings achieved the total synthesis. The lactosaminyl fluoride **159** derived from the corresponding triazole reacted with the disaccharide in the presence of $BF_3 \bullet OEt_2$ to afford a tetrasaccharide **160**. Two glycosylation reactions of glycosyl fluorides followed by α-fucosylation gave the desired trimeric Le^X **162**.



Scheme 79

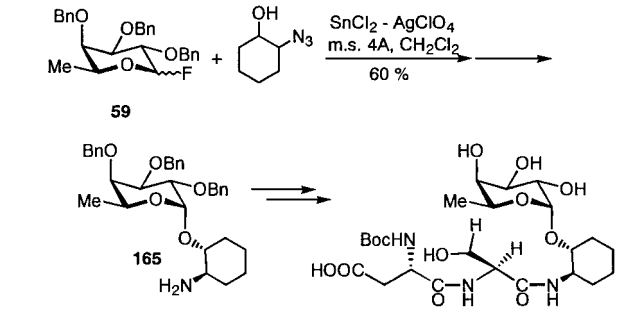
In this context, Wong and coworkers designed **164** and **166** as the model compounds of SLe^X.[77,78] The sugar lactone shown in Scheme 80 reacted with **59** under $SnCl_2$/$AgClO_4$ system to afford disaccharide **163** in 58% yield along with its β-anomer (18%). The compound **163** was deprotected to give SLe^X mimetic **164**.



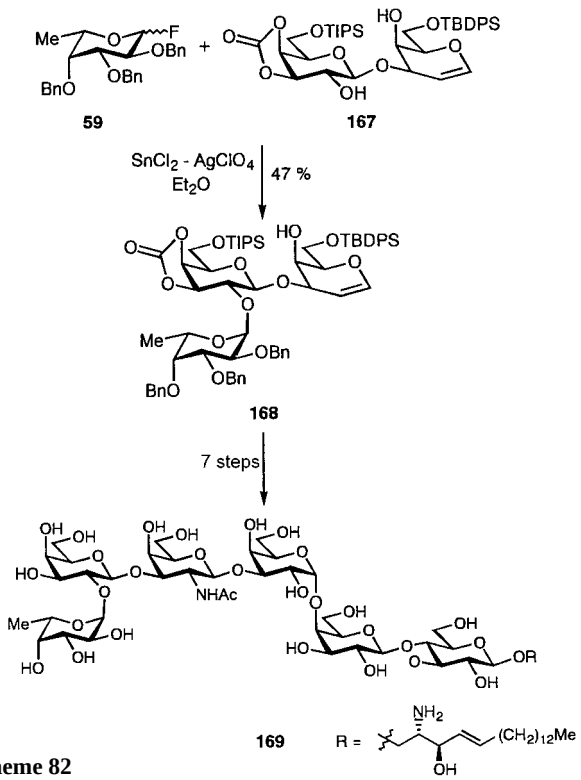
Scheme 80

Another mimetic compound **166** was prepared as follows. L-Fucosyl fluoride **59** was reacted with 2-azidocyclohexanol to give the corresponding *O*-glycoside, which was reduced easily to give amine **165**. With amidation followed by deprotection, the desired compound **166** was obtained (Scheme 81).

With use of a glycal compound, the total synthesis of a human breast tumor associated antigen (MBr1 antigen) was achieved.[79] The coupling of fucosyl fluoride **59** with glycal **167** led to the compound **168** in 47% yield. The fol-



Scheme 81

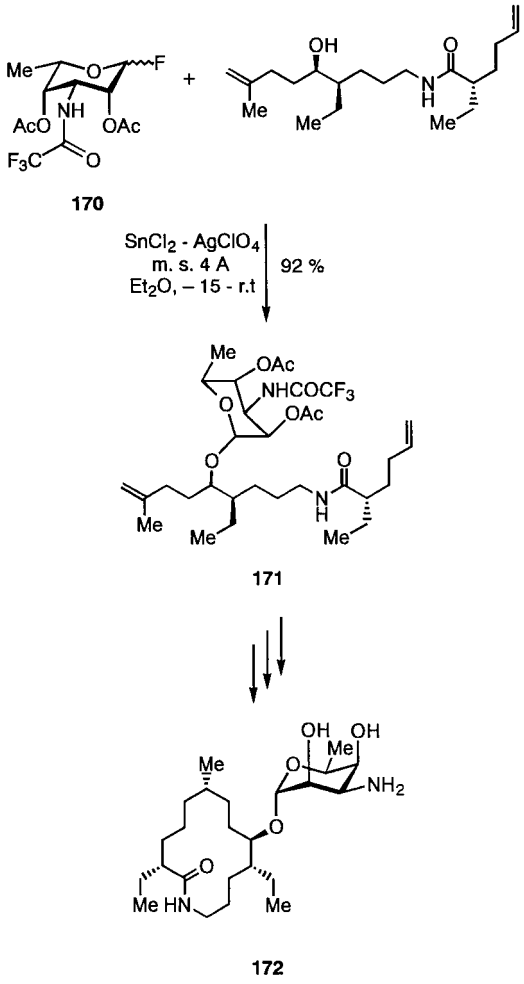


Scheme 82

lowing 7 steps converted compound **168** into MBr1 antigen **169** (Scheme 82).

The antifungal agent Sch 38546 known as fluvirucin B_1 was also synthesized in $SnCl_2/AgClO_4$ system.[80] Diastereoselective glycosylation was carried out with the fluoride **170** and diene carbinol to afford *O*-glycoside **171** in 92% yield. Mo-catalyzed ring closure followed by deprotection afforded Sch 38516 (**172**) in good yield (Scheme 83).

Synthesis of cyclomaltohexaose was conducted by the use of glycosyl fluorides in 21 steps.[81] The fluoride **173** was coupled with a glycosyl donor to afford tetrasaccharide **174** and its α-isomer in 80% yield with the ratio of α/β = 64:36. After deacetylation, elongation of **175** was carried out under $SnCl_2/AgOTf$ system to afford a key glycosyl fluoride **177**. The last glycosidation followed by deprotection was performed to give cyclohexaose **178** in 21% yield (Scheme 84).



Scheme 83

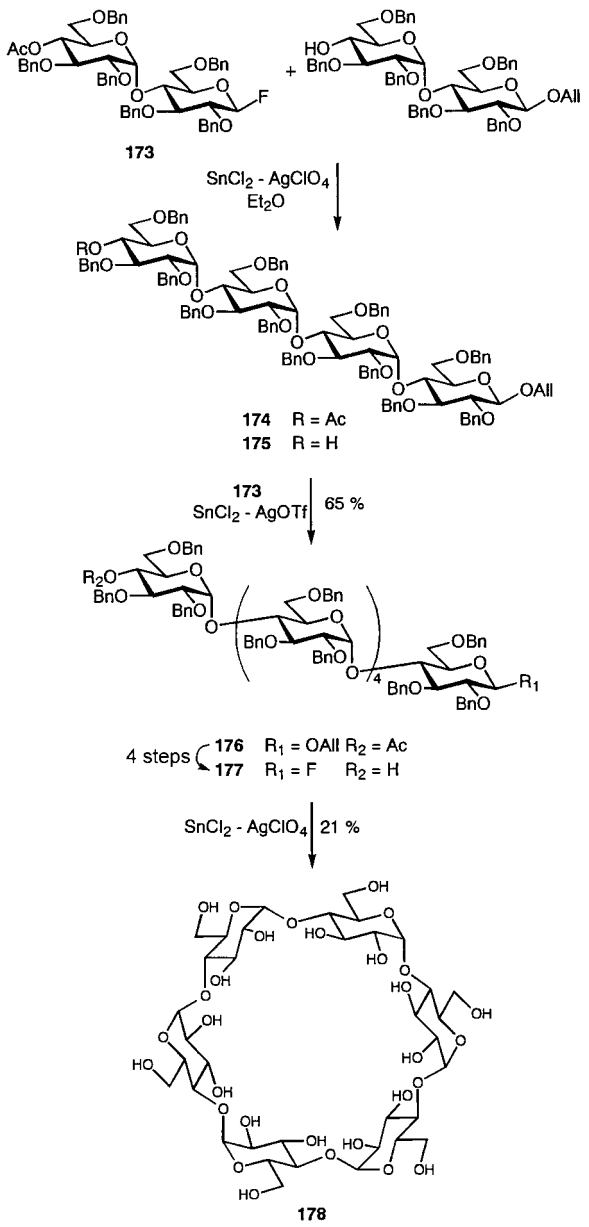
4.3 Cp_2MCl_2/AgX (M = Hf Zr; X = ClO_4, OTf)

Oligosaccharide synthesis using $Cp_2HfCl_2/AgClO_4$ by Ogawa and coworkers is a typical pattern of the reaction between the glycosyl fluoride and Hf reagent system.[82] The general strategy is indicated in Scheme 85.

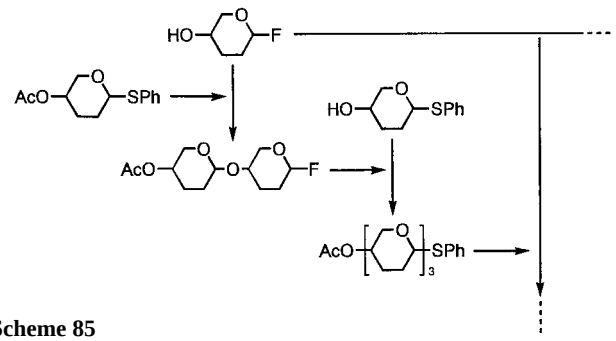
The synthesis of heptasaccharide **186** adopting this method is given in Scheme 86.[82] Disaccharide **181** was derived from thioglycoside **179** under condition a. Elongation was carried out by the reaction of fluoride **181** with acceptor **182** in the presence of $Cp_2HfCl_2/AgClO_4$ to afford trisaccharide **183**. After one-sugar-elongation, heptasaccharide **186** was constructed by the reaction of thioglycoside **183** with deacetylated fluoride **184**.

Further, the synthesis of pentacosasaccharide **190** was established by using four glycosyl fluorides.[83] Started with disaccharide, all coupling reactions consisted of a glycosyl fluoride in the presence of $Cp_2Hf(OTf)_2$ (Scheme 87).

The biatennary heptasaccharide-asparagine conjugate was also formed by use of $Cp2HfCl_2$ as a catalyst.[84] The glycosyl fluoride **191** prepared from mannosyl bromide was allowed to react with a sugar acceptor smoothly to

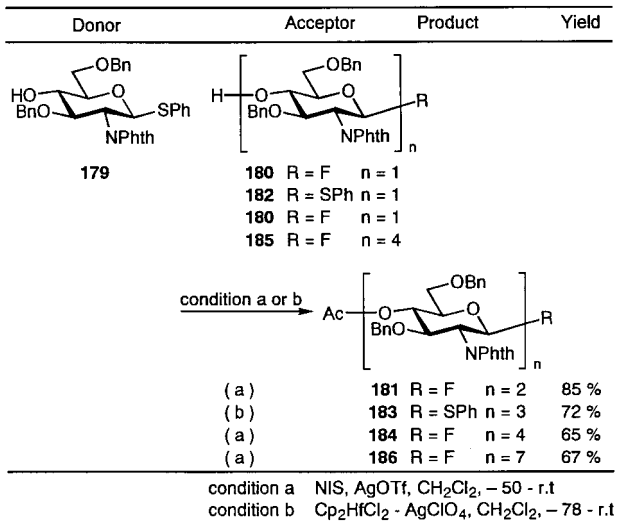


Scheme 84

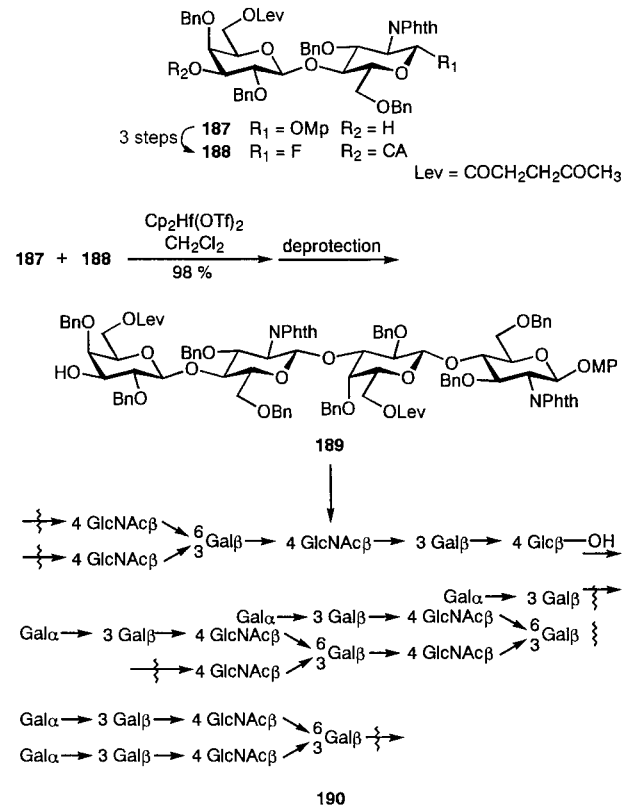


Scheme 85

give trisaccharide **192** in 76% yield. After a 6-step procedure containing two couplings reaction of sugars, the benzylated heptasaccharide-asparagine conjugate **193** was obtained (Scheme 88).

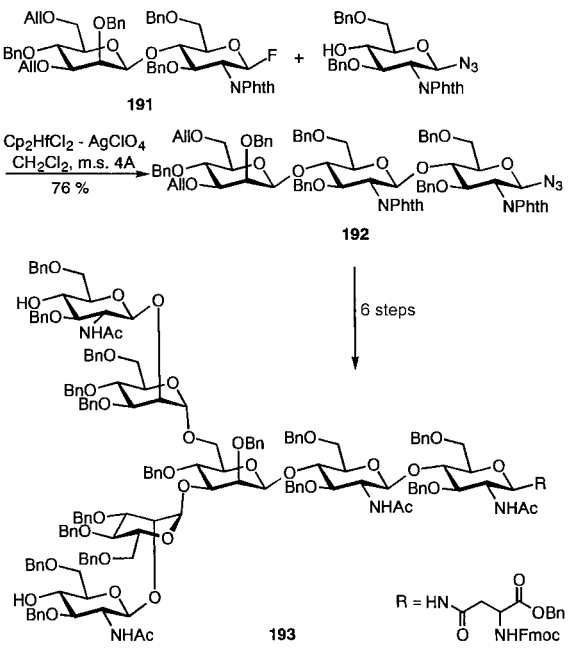


Scheme 86

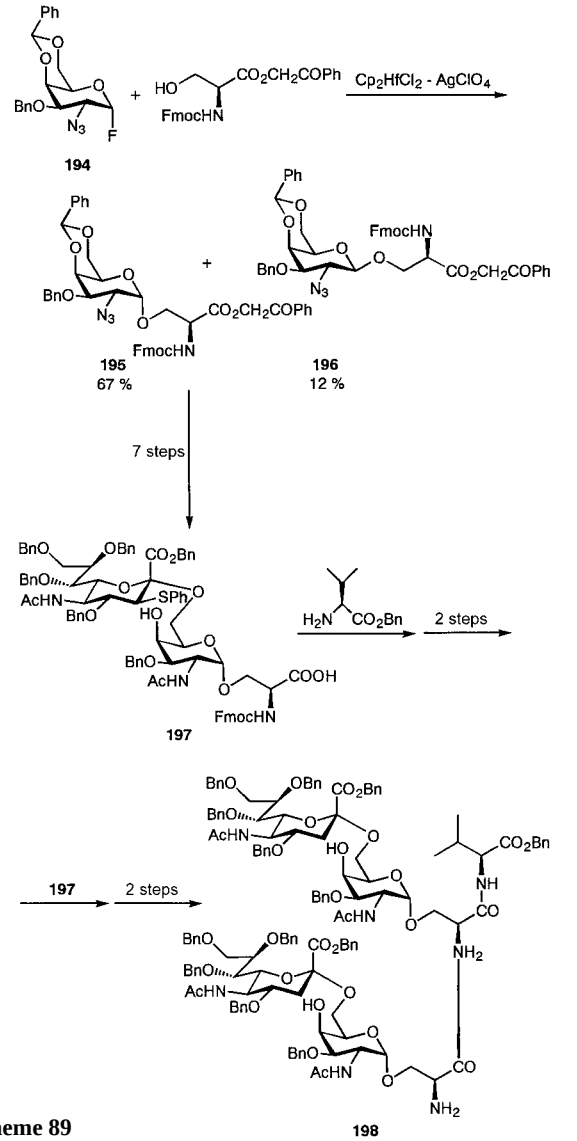


Scheme 87

A partial structure of glycophorin A was constructed in 21 steps by utilizing glycosilation of the fluoride **194**[85, 86](Scheme 89). The α-fluoride **194** was coupled with L-serine derivatives using $Cp_2ZrCl_2/AgClO_4$ as a promotor in CH_2Cl_2 to give the α-glycoside **195** and its β-isomer. When Cp_2HfCl_2 was applied in place of Cp_2ZrCl_2, the α-glycoside **195** was obtained in 67% yield together with β-isomer **196** (12%). After a 7-step-transformation disaccharide **197** was obtained. The compound **197** was condensed with L-valine derivative followed by coupling with disaccharide to give the desired partial structure of glycopforin **198**.

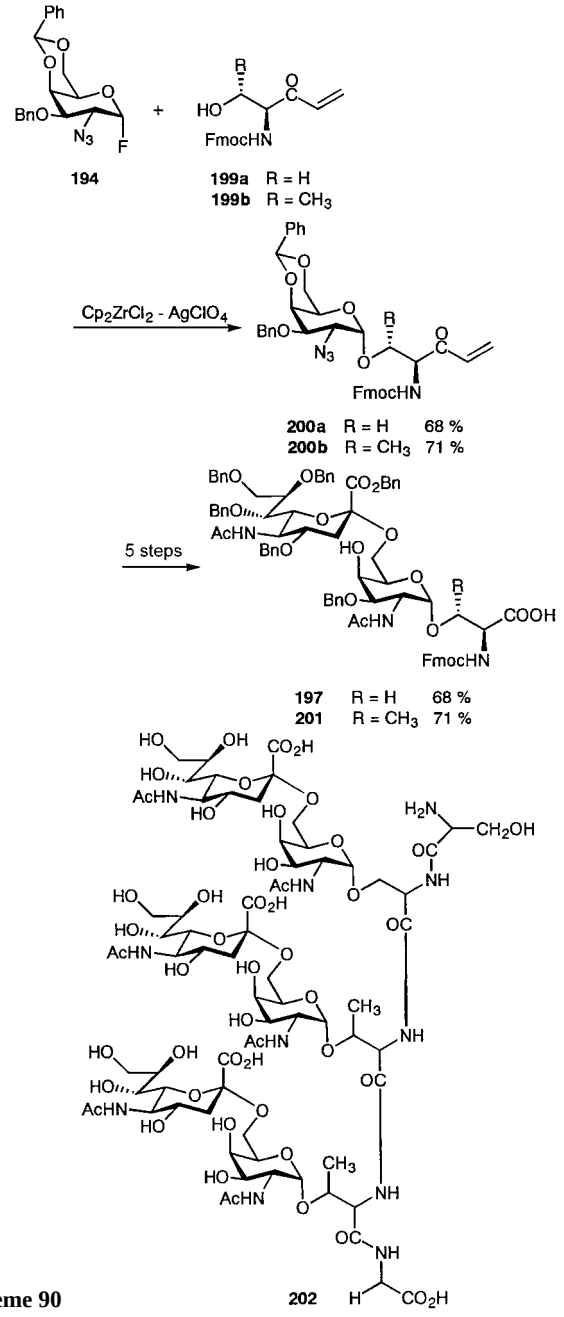


Scheme 88



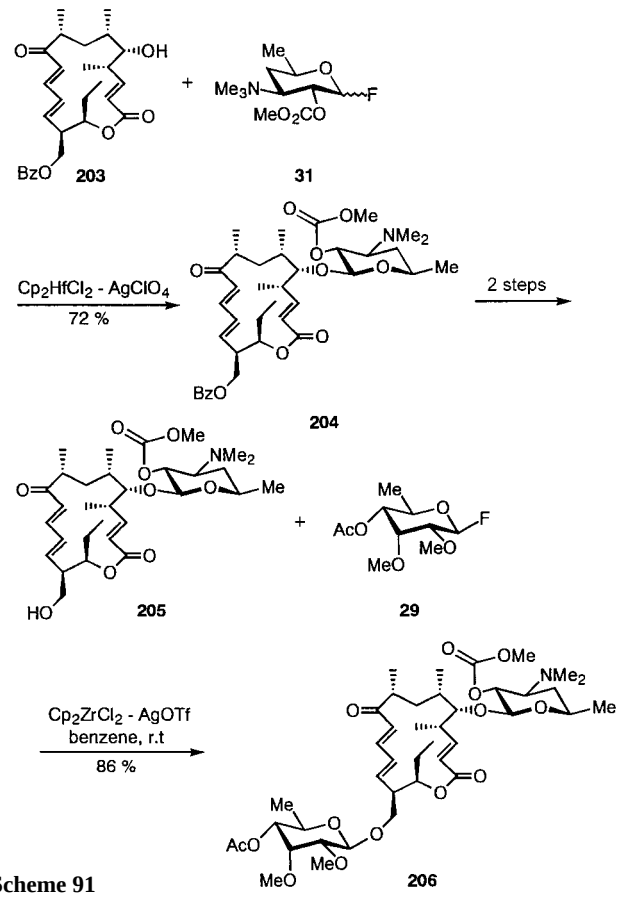
Scheme 89

In this context, an effective synthetic method was developed to prepare *N*-terminal glycopentapeptides.[87] The glycosidation of protected L-selin **199a** or L-threonine **199b** with the glycosyl fluoride **194** was carried out under $Cp_2ZrCl_2/AgClO_4$ and followed by 5-step-reaction to convert into disaccharide **197** or **201**, which was then conjugated to *N*-terminal glycopentapeptides **202** (Scheme 90).

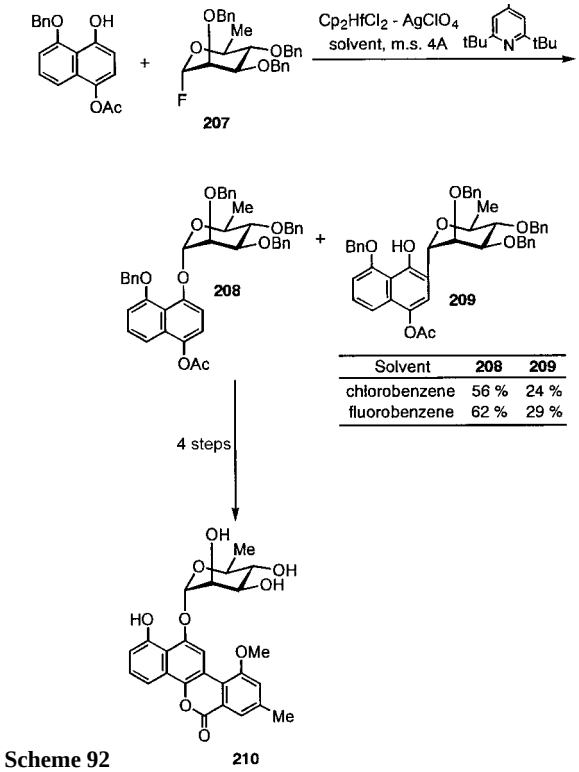


Scheme 90

Suzuki and coworkers made the first total synthesis of Mycinamicin IV **206** using $Cp_2MCl_2/AgClO_4$ (M = Hf, Zr) as promoters.[88] Mycinamicin IV is comprised of two glycosyl bonds, which needed two glycosidations for its construction. One was achieved by Cp_2HfCl_2 and the other by Cp_2ZrCl_2 (Scheme 91).

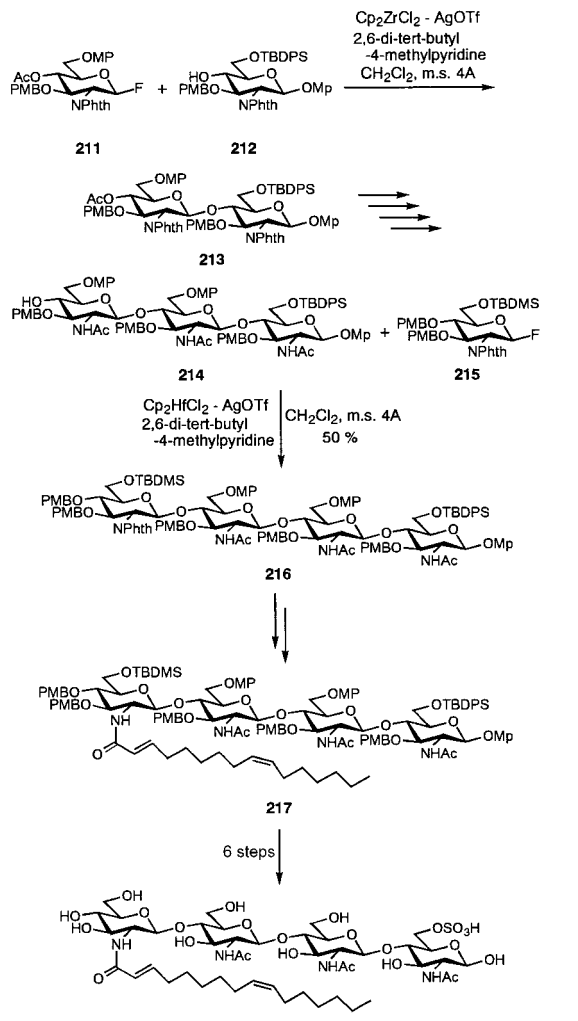


Scheme 91



Solvent	208	209
chlorobenzene	56 %	24 %
fluorobenzene	62 %	29 %

Scheme 92

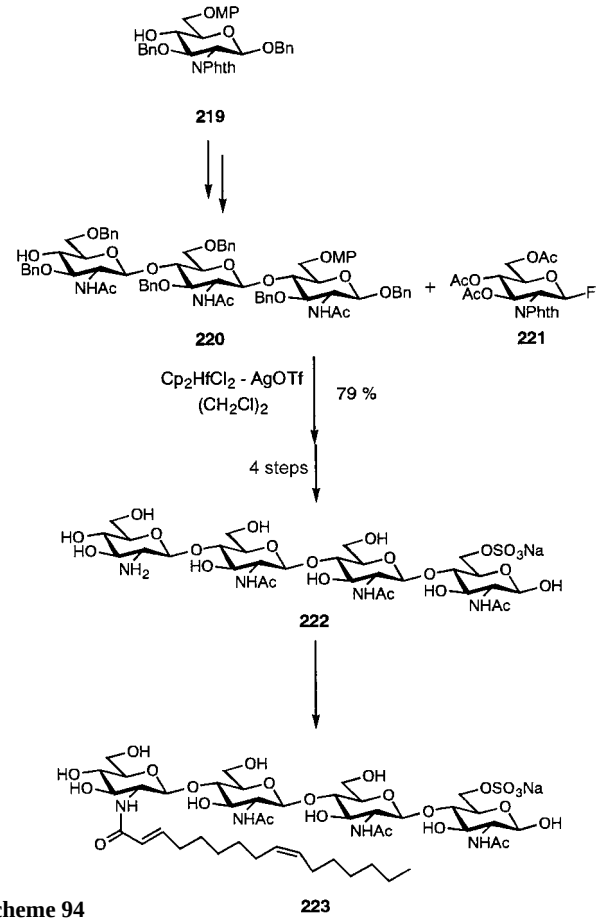


Scheme 93

Later, Suzuki and coworkers synthesized an antibiotic BE-12406A (**210**) via **208**, prepared by the reaction of a naphthol derivative with glycosyl fluoride **207** under activation of $Cp_2HfCl_2/AgClO_4$.[89] At the stage of *O*-glycosidation, $SnCl_2/AgClO_4$, TMSOTf, or BF_3•OEt_2 was employed in place of $Cp_2HfCl_2/AgClO_4$, but they uniformly gave *C*-glycoside **209**. From the result of the solvent effect, halogenated aromatic solvents such as chlorobenzene and fluorobenzene were chosen (Scheme 92).

Two total syntheses of NodRm-IV (S) were reported recently. The first synthesis was achieved by Nicolaou and coworkers in 1992.[90] Starting with *O*-glycosidation of the fluoride **211**, the pathway included two reactions of glycosyl fluorides. After the carbohydrate skeleton was completed, an alkyl chain was substituted followed by deprotection to give the desired compound, NodRm-IV(S) **218** (Scheme 93).

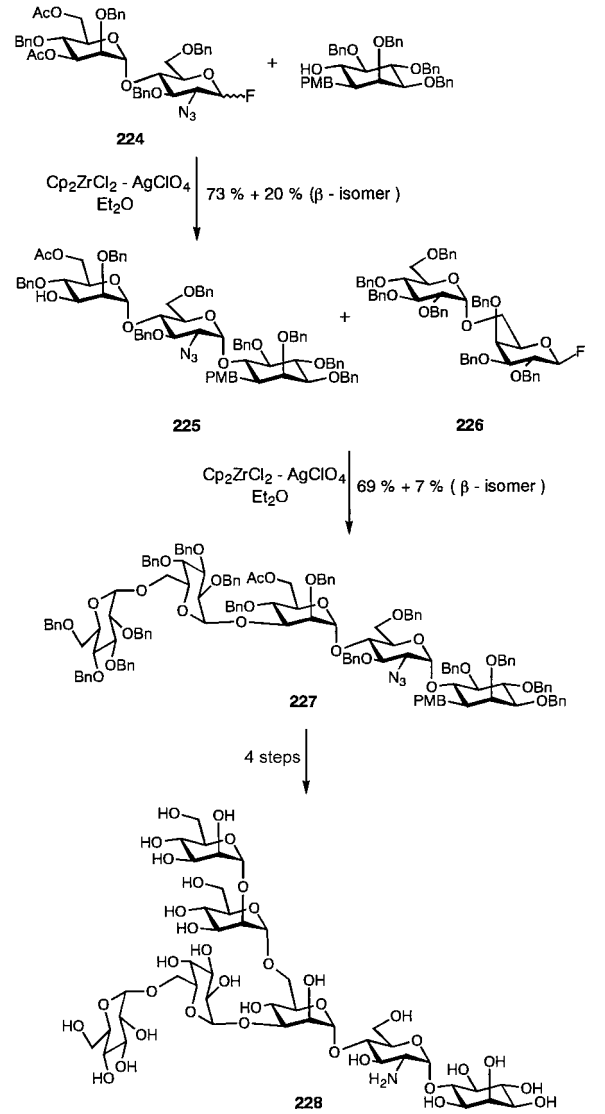
The second report is that of Ogawa and his coworkers in 1994.[91] The trisaccharide **220** was obtained by the reaction of monosaccharide **219** with a glycosyl donor followed by deprotection and acetylation. The fluoride **221** was coupled with compound **220** in the presence of a $Cp_2HfCl_2/AgOTf$ system. While alkylation was demonstrated before deprotection in Nicolaou's strategy, Ogawa designed a key intermediate **222** containing free OH groups before alkylation (Scheme 94).



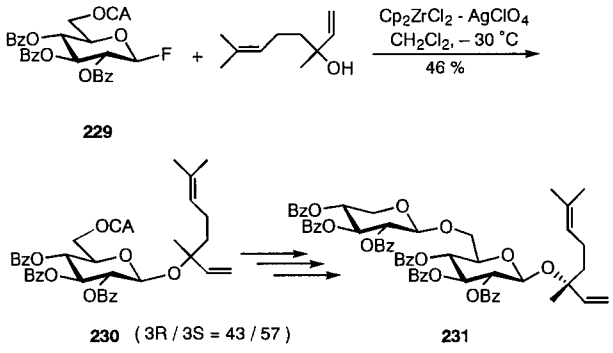
Scheme 94

The synthesis of hexasaccharide of glycophosphatidyl inositol (GPI) anchor was developed using glycosyl fluoride as a sugar donor.[92] The fluoride **224** was converted into compound **225** by a successive treatment of $Cp_2ZrCl_2/AgClO_4$ and deacetylation. The other fluoride **226** was coupled with derived compound **225** in the presence of $Cp_2ZrCl_2/AgClO_4$ to give tetrasaccharide **227** in 69% yield along with its β-epimer (7%). After 4 steps, the desired hexasaccharide **228** was obtained (Scheme 95).

The synthesis of neohancoside A was comprised of the reaction of linalool with a glycosyl fluoride under $Cp_2ZrCl_2/AgClO_4$.[93] Glycosylation of prepared glycosyl fluoride **229** with racemic linalool led to linalyl glycoside **230** in 46 % yield. Deprotection of the chloroacetyl group, and separation of the diastereoisomer followed by debenzoylation provided monoterpene diglycoside, neohancoside A **231** (Scheme 96).



Scheme 95



Scheme 96

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