Recent Progress in *O*-Glycosylation Methods and Its Application to Natural Products Synthesis

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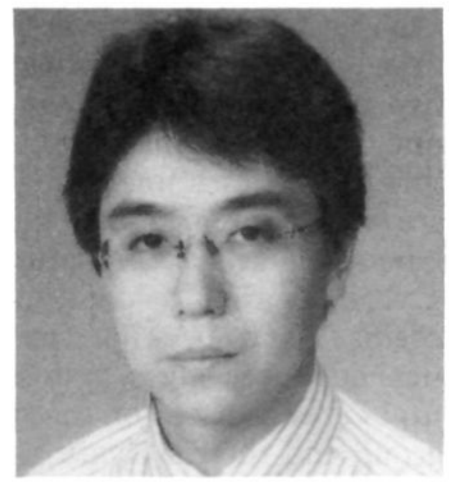

Kazunobu Toshima was born in Japan in 1960. He was graduated from Keio University, where he also received his Ph.D. in 1988 under the direction of Professor Mitsuhiro Kinoshita. His thesis is entitled *Total Synthesis of Elaioplylin* (*Azalomycin B*). After one year as a postdoctoral fellow at University of Pennsylvania with Professor K. C. Nicolaou (now at the Scripps Research Institute and University of California, San Diego), he joined the Department of Applied Chemistry of Keio University in 1989. His current research interests focus on the development of new synthetic organic methodologies, particularly for *O*- and *C*-glycosylation methods, total synthesis of bioactive natural products, and the pursuit of DNA-interactive molecules such as an artificial restriction enzyme.

Kuniaki Tatsuta received his Ph.D. from Keio University in 1969 working under the direction of Prof. S. Umezawa and joined the faculty as an assistant. He was promoted to a professor of the Department of Applied Chemistry, Keio University in 1986, and he then moved to the Institute of Microbial Chemistry in 1991 and then to Waseda University in 1993. He was a postdoctoral fellow at Harvard University with Prof. R. B. Woodward from 1973 to 1975 and a visiting professor of Cambridge University in 1988. He has received several awards including the Divisional Award of the Chemical Society of Japan (1986) and the Award of the Japan Antibiotics Research Association (1988). His research program focuses on the study of total syntheses of natural products, especially useful antibiotics, and the applications of these studies to the bioorganic simulations of their biosyntheses. Also, his research includes the developments of new antibiotics and medicines. In 1988, his anticancer agent, THP-adriamycin was marketed.

I. Introduction

Recently, an enormous amount of precise biological studies of naturally occurring products such as membranes, cell walls, and antibiotics and the mechanisms of action of these substances have shed light on the biological significance of the glycons of glycoconjugates (glycoproteins, glycolipids) and antibiotics in molecular recognition for the transmission of biological information.[1] With the stimulant biological background, the *O*-glycosylation method, which is a crucial synthetic organic methodology to attach sugar to the other sugar moieties or other molecules (aglycon), is again becoming more and more important. Since the major historical advance of the Koenigs–Knorr method was shown in 1901, considerable attention has been directed toward the efficiency of the *O*-glycosylation method. From a synthetic standpoint, the efficiency of the *O*-glycosylation reaction generally involves a high chemical yield, regioselectivity, and stereoselectivity. Among them, high regioselectivity was easily realized by the selective

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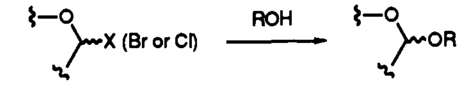
protection of the hydroxyl group of the glycosyl acceptor. Therefore, many organic chemists have focused on the high chemical yield and high stereoselectivity of this reaction. This review concentrates on the new progress in *O*-glycosylation methods after 1980 including historically indispensable protocols before 1980. Some selected elegant applications of a glycosylation reaction for the synthesis of biologically attractive natural products are also included. This article mainly deals with the development of new glycosyl donors with specific functionality and their activating methods. However, since the general aspects of the *O*-glycosylation method have been very well reviewed in the past,[2] the present article particularly emphasizes the recent special approach to the highly stereoselective syntheses of (1) 2-deoxyglycosides and (2) β-D-mannoglycosides, both of which having had difficult problems for a long time in this field. 2-Deoxyglycosides are widely found in biologically important natural products, especially in antitumor antibiotics. β-D-Mannoglycosides are indispensable substances in the glycoproteins. For a survey on the general current methodological advances, glycosyl donors are roughly classified into 14 groups based on the type of anomeric functional group and their activating methods which are discussed in an earlier part of this review: (1) glycosyl halide, (2) thioglycoside, (3) 1-*O*-acyl sugar, (4) ortho ester, (5) 1-*O*- and *S*-carbonate, (6) trichloroimidate, (7) 4-pentenyl glycoside, (8) phosphate derivative, (9) 1-*O*-sulfonyl glycoside, (10) 1-*O*-silylated glycoside, (11) 1,2-anhydro sugar, (12) 1-hydroxyl sugar, (13) glycal, and (14) others. Further new attractive concepts in this area include (1) armed sugar–disarmed sugar, (2) conformational assistance of glycosyl donor, and (3) double stereodifferentiation in glycosylation are also reviewed in detail in the last section.

II. Glycosyl Halide

A. Glycosyl Bromide and Chloride

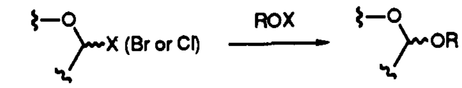
The use of glycosyl bromide or chloride as an effective glycosyl donor in the glycosylation reaction was first introduced by Koenigs and Knorr in 1901.[3] In relation to the anomeric stereochemistry of the glycosylation reaction, three significant basic methods, the neighboring group assisted method for construction of 1,2-*trans*-glycosides such as β-gluco or α-manno type glycoside, the in situ anomerization method[4] for synthesis of α-gluco or α-manno type glycoside, and the heterogenic catalyst method[5] for preparation of β-mannoglycoside (see section XVI.B) were developed in this area.[2d,f] The well-known classical Koenigs-Knorr method used heavy metal salts (mainly silver and mercury salts) as activating reagents. A variety of heavy metal salts such as AgOTf, Ag_2O, Ag_2CO_3, $AgClO_4$, $AgNO_3$, Ag–silicate, $Hg(CN)_2$, $HgBr_2$, $HgCl_2$, and HgI_2[6] and their combined use were employed in this area (Table 1).[2a–h,j,l] The order of reactivity of some representative catalysts was generally confirmed.[2d–f] Further, Ag_2CO_3, Ag_2O, HgO, $CdCO_3$, *S*-collidine, and TMU were frequently used as an acid scavenger and water was generally removed by Drierite and molecular sieves during these glycosylation reactions.[2a–h,j,l] On the other hand, other glycosylation methods using glycosyl bromide and chloride in the absence of any metal were also widely studied. Lemieux and co-workers[7a] introduced a mild glycosylation in the presence of Bu_4NBr and one of the most representative applications of this method led to the elegant syntheses of several blood group antigenic determinants.[7b–d] Also, the glycosylation reactions which involved a transformation of glycosyl bromide into the corresponding onium salts by Et_3N, Ph_3P, and Me_2S were developed by Schuerch and coworkers.[8] Further, several Lewis acids such as $SnCl_4$,[9] $BF_3{\cdot}Et_2O$,[9] $Sn(OTf)_2$–collidine,[10a] $Sn(OTf)_2$–TMU[10b] and TrCl–$ZnCl_2$[11] produced nontoxic and nonexplosive activating reagents of their halides in this field (Table 2). The glycosylations of aryl alcohols using a phase-transfer catalyst such as $Et_3N^+CH_2PhBr^-$,[12a,b] $Et_3N^+CH_2PhCl^-$,[12c] $Me(CH_2)_{15}N^+Me_3Br^-$,[12d] $Bu_4N^+Br^-$,[12e] or $Bu_4NH^+SO_4^-$ [12f] were also developed (Table 3). Recently, Sasaki et al.[13] offered a new glycosylation method using glycosyl bromide in the presence of hindered amines such as 2,6-lutidine or TMU under high-pressure conditions. Nishizawa and his co-workers[14] developed a thermal glycosidation of glycosyl chloride in the presence of TMU as an acid scavenger without any metal salts and the method was effectively applied to their synthesis of cyclo-L-rhamnohexose[14e] which was the first cyclooligosaccharide of the L series.

Table 1. Glycosidation of Glycosyl Bromide or Chloride by Use of Heavy Metals



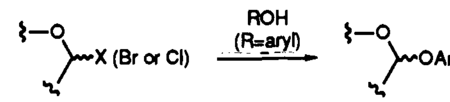
activator	acid scavenger	drying agent	ref(s)
$AgClO_4$	Ag_2ClO_3	Drierite	2a–h,j,l, 6
AgOTf	Ag_2O	molecular sieves	
$AgNO_3$	HgO		
Ag_2CO_3	$CdCO_3$		
Ag_2O	*s*-collidine		
$Hg(CN)_2$	TMU		
$HgBr_2$			
$NgCl_2$			
HgI_2			

Table 2. Glycosidation of Glycosyl Bromide or Chloride by Use of Lewis Acid



activator	X	ref
$SnCl_4$	$SnBu_3$	9
$BF_3{\cdot}OEt_2$	$SnBu_3$	9
$Sn(OTf)_2$–collidine	H	10a
$Sn(OTf)_2$–TMU	H	10b
TrCl–$ZnCl_2$	H	11

Table 3. Glycosidation of Glycosyl Bromide or Chloride by Phase-Transfer Catalyst

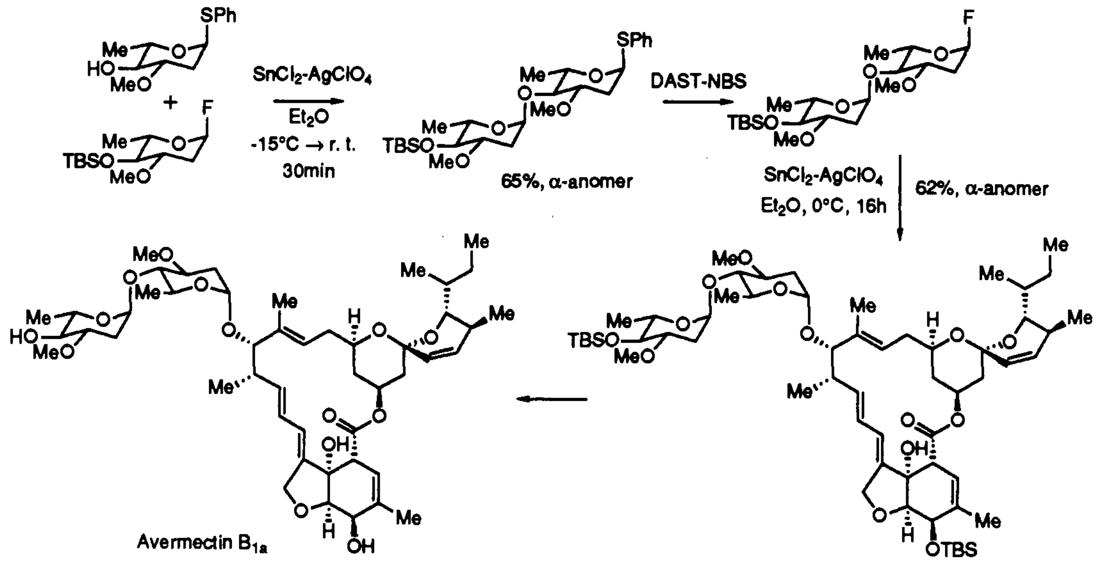


catalyst	conditions	ref(s)
$Et_3N^+CH_2PhBr^-$	$CHCl_3/H_2O/NaOH$	12a,b
$Et_3N^+CH_2PhCl^-$	CH_2Cl_2/H_2O/NaOH or KOH	12c
$Me(CH_2)_{15}N^+Me_3Br^-$	$CH_2Cl_2/H_2O/NaOH$	12d
$Bu_4N^+Br^-$	$CH_2Cl_2/H_2O/NaOH$	12e
$BuN^+HSO_4^-$	CH_2Cl_2/H_2O/ NaOH or $NaHCO_3$	12f

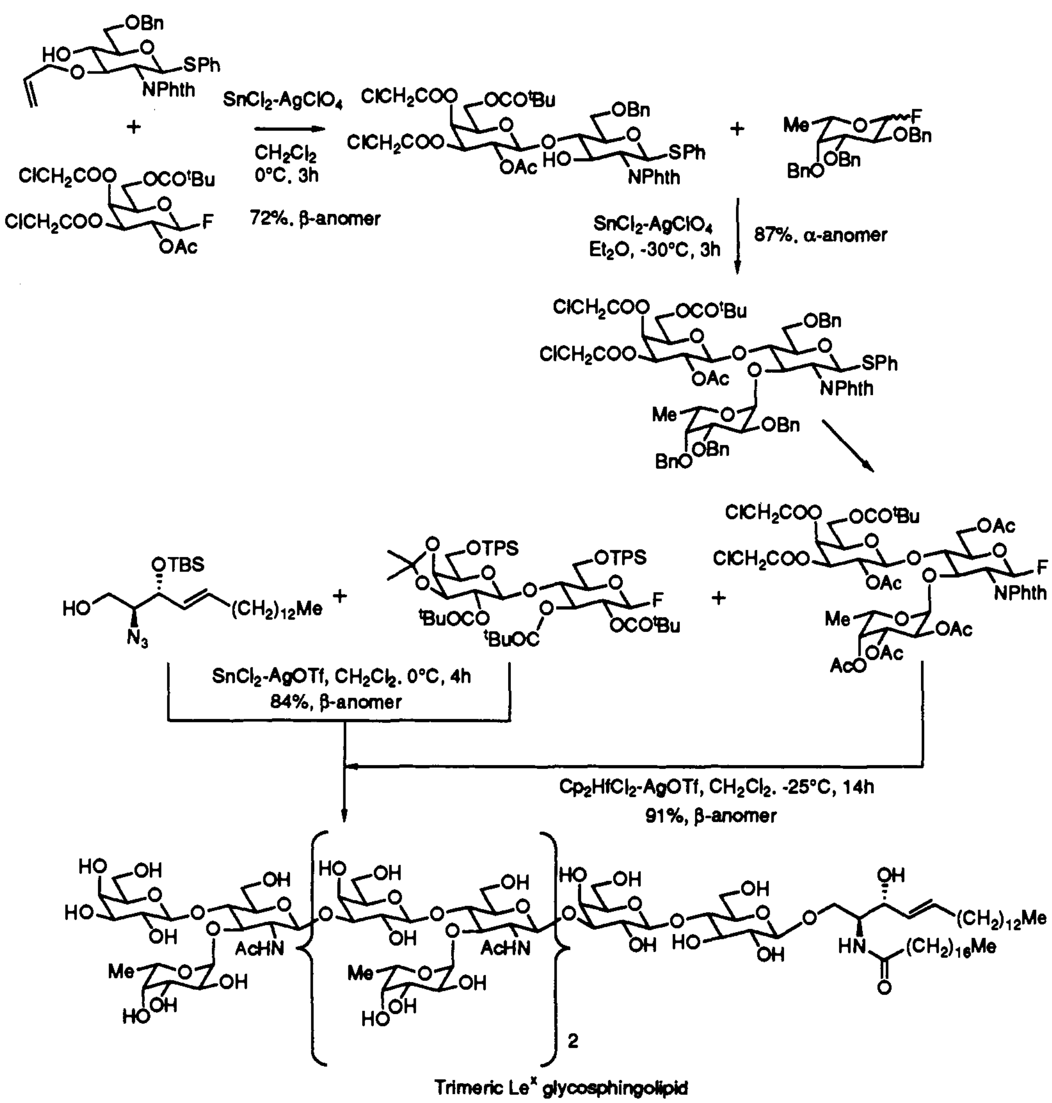
B. Glycosyl Fluoride

The use of glycosyl fluoride as a glycosyl donor with a fluorophilic activator, $SnCl_2$–$AgClO_4$, was first introduced by Mukaiyama et al. in 1981.[15] After the first great advance in this field, Nicolaou and his co-workers[16] made extensive studies of its application in the synthesis of natural products such as avermectin[16a] including the useful preparation of glycosyl fluoride from another glycosyl donor, thioglycoside (Scheme 1). One of the

Scheme 1

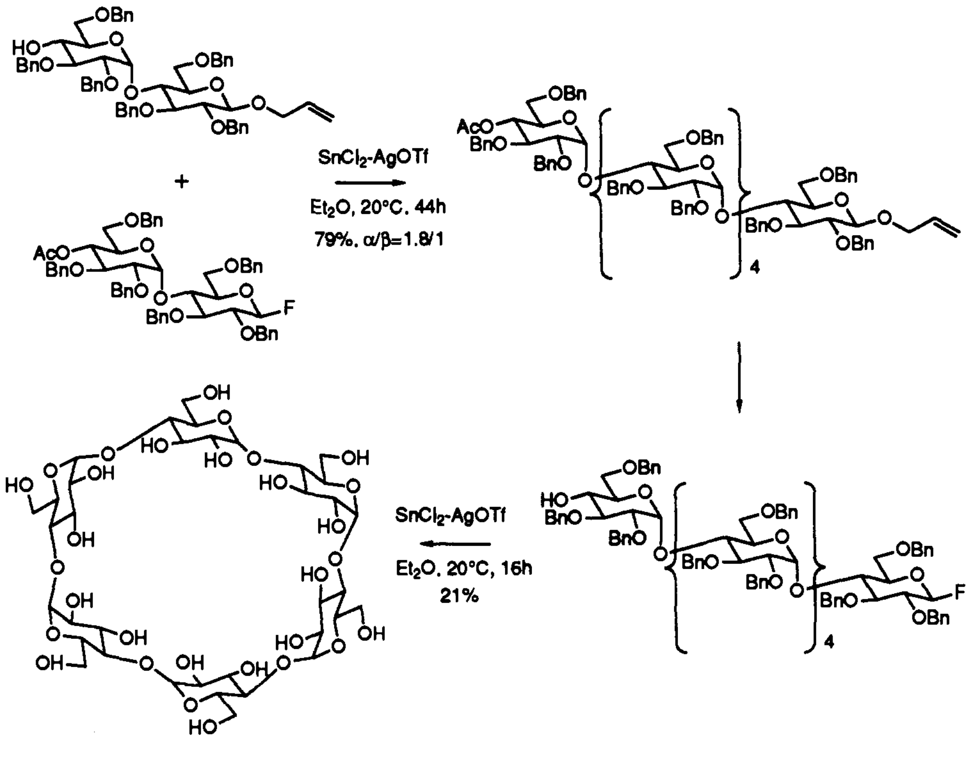


Scheme 2



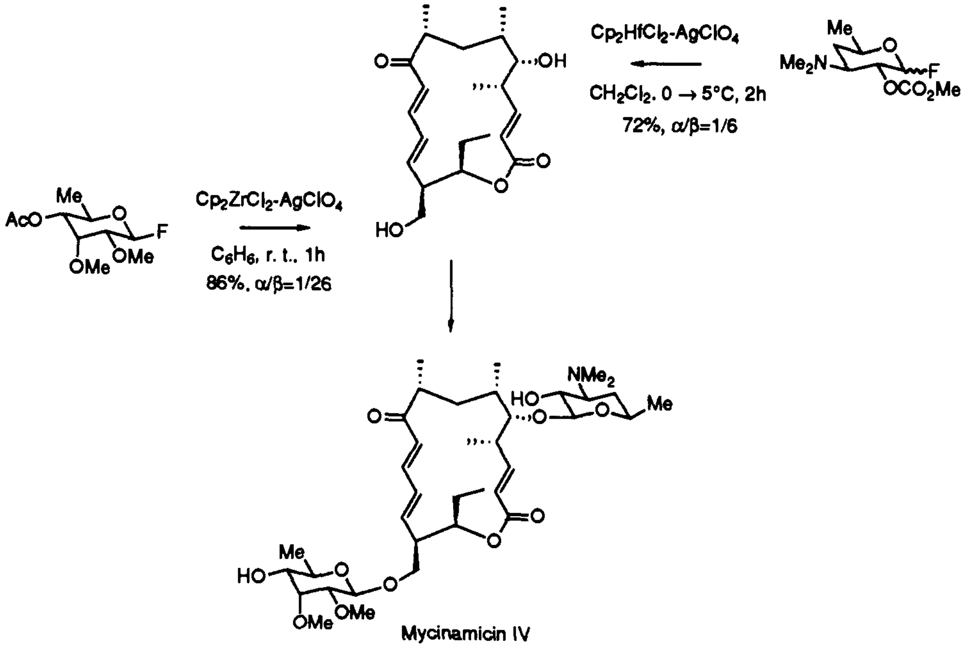
Trimeric Le^x glycosphingolipid

Scheme 3



α-Cyclodextrin

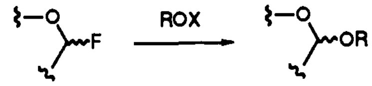
Scheme 4



Mycinamicin IV

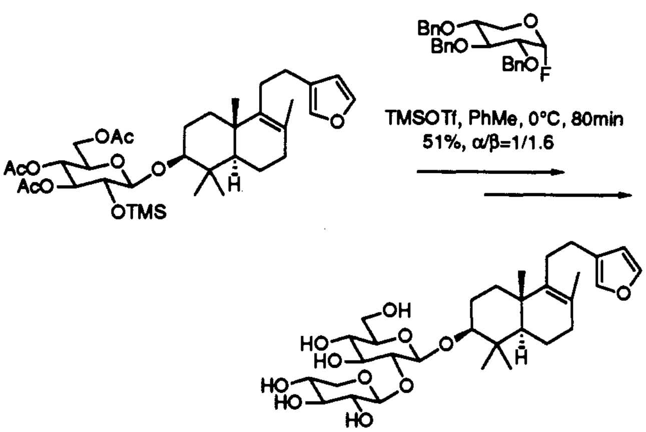
notable advantages of the glycosyl fluoride as a glycosyl donor is due to its higher thermal and chemical stability as compared to the low stability of other glycosyl halides. Therefore, glycosyl fluoride can be generally purified by an appropriate distillation and even by column chromatography with silica gel. Having such favorable synthetic attributes, a number of specific fluorophilic reagents were developed (Table 4), for instance $SnCl_2$–$TrClO_4$ (Mukaiyama et al.),[17] SiF_4 (Noyori et al.),[18] TMSOTf (Noyori et al.),[18] $BF_3 \cdot Et_2O$ (Nicolaou et al.,[19a] Kunz et al.,[19b,c] and Vozny et al.[19d]), TiF_4 (Thiem et al.),[20] SnF_4 (Thiem et al.),[20] Cp_2MCl_2–$AgClO_4$ (M = Zr, Hf; Suzuki et al.),[21] Cp_2ZrCl_2–$AgBF_4$ (Suzuki et al.),[22] Cp_2HfCl_2–AgOTf (Suzuki et al.[22] and Nicolaou et al.[23]), Me_2GaCl (Kobayashi et al.),[24] and Tf_2O (Wessel et al.).[25] The initial promoter, $SnCl_2$–$AgClO_4$, was effectively applied to Nicolaou's syntheses[23,26] of several types of glycosphingolipids (Scheme 2) and Ogawa's cyclodextrin synthesis (Scheme 3).[27] Also, Suzuki and his coworkers[21c] elegantly applied their original activators, Cp_2MCl_2–$AgClO_4$ (M = Zr, Hf), to their total synthesis of mycinamicin IV (Scheme 4). Nishizawa et al.[28]

Table 4. Glycosidation of Glycosyl Fluoride



activator	X	ref(s)
$SnCl_2$–$AgClO_4$	H	15, 16
$SnCl_2$–$TrClO_4$	H	17
TMSOTf (cat.)	TMS	18
SiF_4 (cat.)	TMS	18
$BF_3{\cdot}Et_2O$	H	19
TiF_4	H	20
SnF_4	H	20
Cp_2MCl_2–$AgClO_4$ (M = Zr or Hf)	H	21
Cp_2ZrCl_2–$AgBF_4$	H	22
Cp_2HfCl_2–AgOTf	H	22, 23
Me_2GaCl	H	24
Tf_2O	H	25

Scheme 5



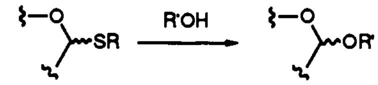
Baiyunoside

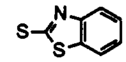
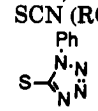
employed Noyori's reagent, TMSOTf, in their baiyunoside synthesis (Scheme 5).

III. Thioglycoside

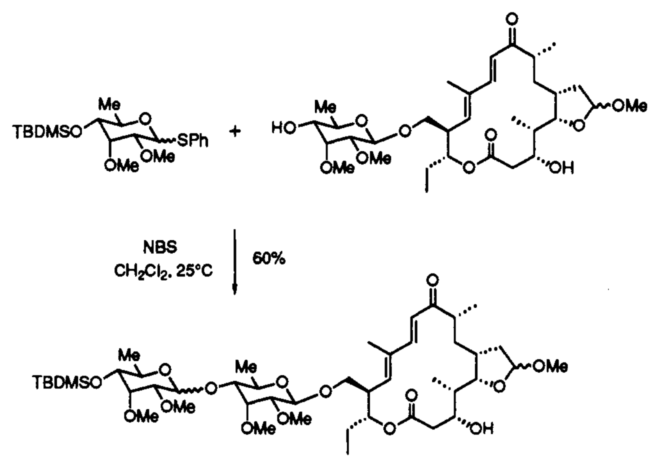
Thioglycosides have been extensively studied as a useful glycosyl donor due to their high stability in many organic operations. Thioglycoside is also a good intermediate for the preparation of the corresponding glycosyl fluoride.[16a] Up to now, several different kinds of alkyl- and arylthio groups, including the heterocyclic thio groups, were developed with their appropriate activating reagents (Table 5). Since Ferrier et al.[29] first introduced a mercury salt, $HgSO_4$, as a glycosylation promoter of thioglycoside, other thiophilic metal salts such as $HgCl_2$ (Ferrier et al.[29] and Wiesner et al.[30]), PhHgOTf (Garegg et al.),[31] $Hg(OBz)_2$ (van Cleve),[32] $Hg(NO_3)_2$ (Hanessian et al.),[33] $Cu(OTf)_2$ (Mukaiyama et al.),[34] and $Pd(ClO_4)_2$ (Woodward et al.)[35,36] appeared in this field. Among them, $HgCl_2$ was employed in Wiesner's digitoxin synthesis[30] (see section XVI.A) and $Pd(ClO_4)_2$ was effectively used in Woodward's erythromycin A synthesis[35] and Wuts' synthetic studies of avermectin.[36] Ogawa and his co-workers recently developed the combinational use of $CuBr_2$–Bu_4NBr–AgOTf[37] and the use of PhSeOTf[38] as effective promoters of thioglycosides. The former activator was applied to their glycospingolipids syntheses[37b–d] while the latter promoter was employed in their cycloglycosylations in the mannooligose series.[38c,d] On the other hand, as alternative activation methods without any metal salts, oxidative reagent, Br_2, was used by Koto

Table 5. Glycosidation of Thioglycoside

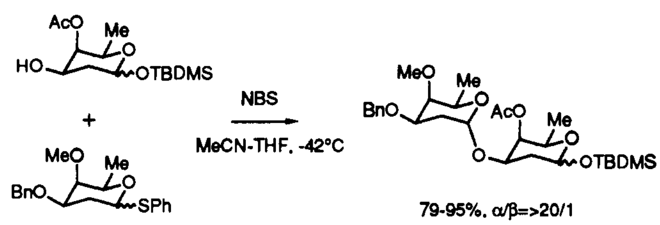


activator	SR	ref(s)
$HgSO_4$	SPh	29
$HgCl_2$	SEt, SPh	29, 30
PhHgOTf	SPh	31
$Hg(OBz)_2$	SPh	32
$Hg(NO_3)_2$	SPy	33
$Cu(OTf)_2$		34
$Pd(ClO_4)_2$	SPy	35, 36
$CuBr_2$–Bu_4NBr–AgOTf	SMe, SEt	37
PhSeOTf	SMe	38
AgOTf–Br_2	SEt	40
NBS	SPh	41
NIS–TfOH	SMe, SEt, SPh	43, 44, 45
IDCP	SEt	46
$NOBF_4$	SMe	47
MeI	SPy	48
MeOTf	SEt	49
MeSOTf	SMe, SEt, SPh	50
DMTST	SMe, SEt, SPh	51, 52
$TrClO_4$ (cat.)	SCN (ROTr)	53
AgOTf		54
TBPA	SEt, SPh	58
–e	SPh	56, 57

Scheme 6

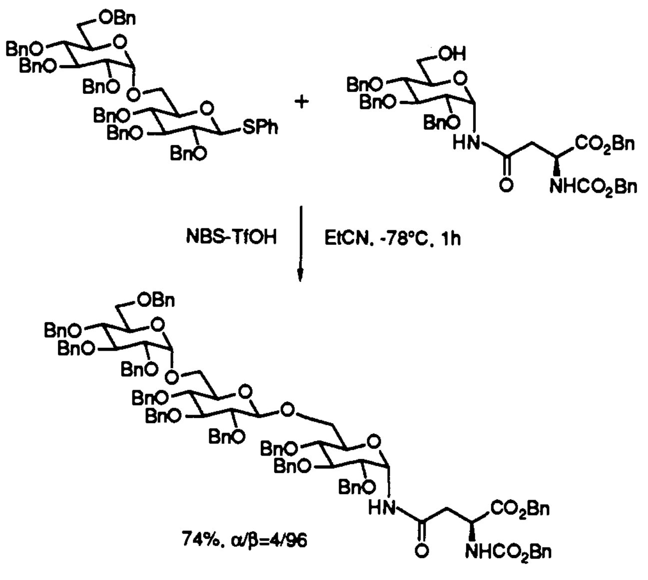


Scheme 7

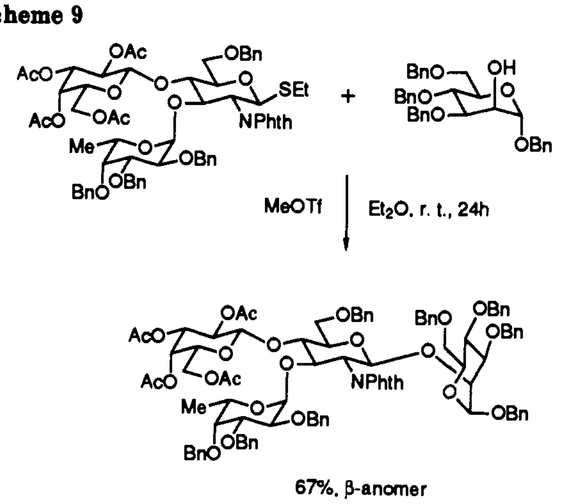


and Zen,[39] and later Kihlberg et al.[40] reported the confirmational use of AgOTf–Br_2 for the in situ activation of ethylthioglycosides. Along this line, Nicolaou and co-workers[41] introduced NBS as a milder and more practical glycosylation promoter of phenyl thioglycosides and the applications were demonstrated in their synthesis of a tylosin derivative[41] (Scheme 6) and the synthesis of the disaccharide moiety of olivomycin A by Roush et al.[42] (Scheme 7). Fraser-Reid et

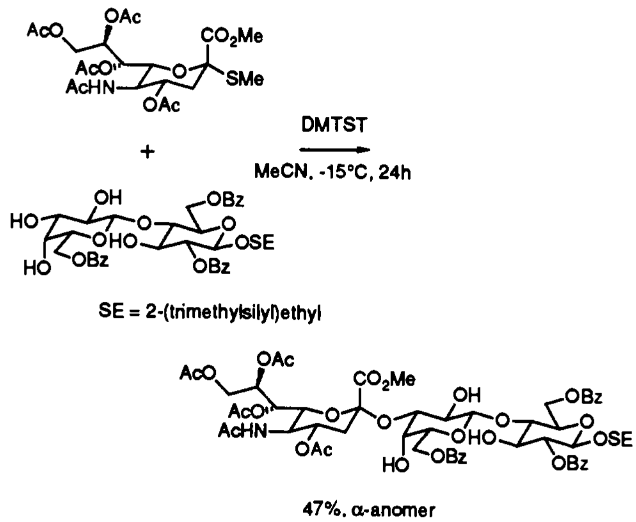
Scheme 8



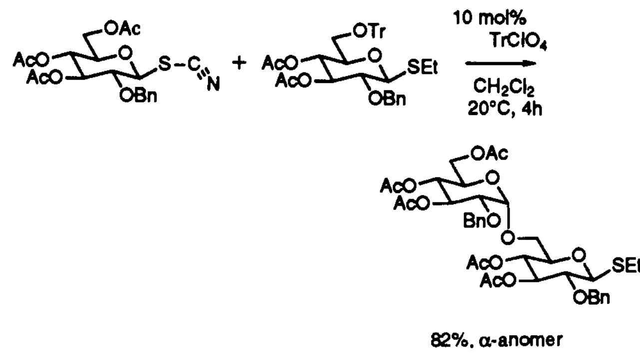
Scheme 9



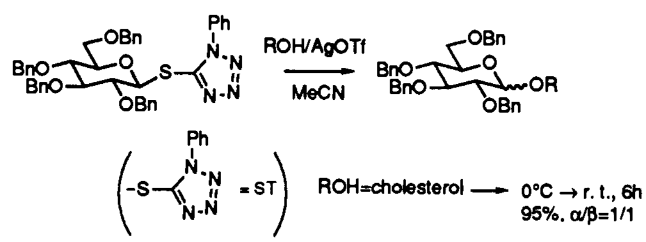
Scheme 10



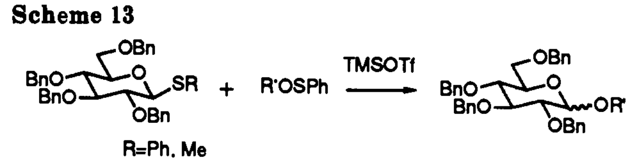
Scheme 11



Scheme 12

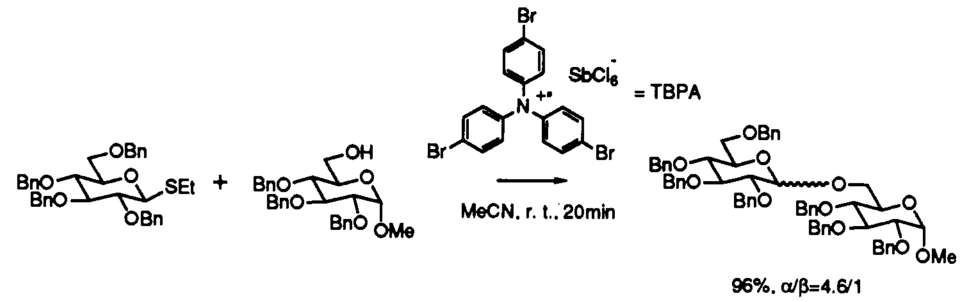


Scheme 13

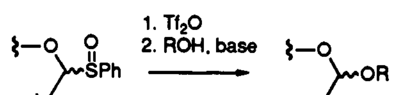


al.[43] and van Boom et al.[44] independently announced NIS–TfOH to effectively activate both disarmed methyl and ethyl thioglycosides. Similarly, Sasaki et al.[45] also reported NBS–TfOH in his synthesis of the oligosaccharide moiety of nephritogenoside (Scheme 8). Further, in the extended glycosylation studies of thioglycosides by van Boom's group,[46] IDCP was found to be an appropriate promoter in the selective glycosylation reaction[46a] of an armed thiosugar and a disarmed thiosugar, the concept of which was originally investigated by Fraser-Reid (see section XVII.A). Another oxidative agent, $NOBF_4$, was introduced by Pozsgay and Jennings.[47] The alkylating agents such as MeI (Mereyala et al.)[48] and MeOTf (Lönn)[49] also offered a new significant entry to the direct activation of thioglycosides. Lönn[49a] reported the synthesis of several oligosaccharides, which were parts of glycoproteins, by MeOTf and ethyl thioglycosides (Scheme 9). Alkyl sulfenyl triflate, MeSOTf, generated from MeSOBr and AgOTf was used in Garegg's glycosylation method.[50] On the other hand, DMTST was first introduced by Fügedi et al.[51] while Hasegawa et al. has widely investigated the glycosidations of sialic acid[52a–c] using DMTST and also applied it to their gangliosides syntheses[52d–g] (Scheme 10). Kochetkov and his coworkers[53] very recently announced the use of a cyanothio group, and Ogura and co-workers[54] have developed a (1-phenyltetrazol-5-yl)thio (ST) group as a new thio functional group at the anomeric position of the glycosyl donor. The former group can be distinguished from ethythio group and effectively activated by a catalytic amount of $TrClO_4$ in the presence of tritylated alcohol to exclusively give 1,2-*cis*-glycosidic linkages (Scheme 11). The latter one can be promoted by AgOTf under mild conditions (Scheme 12). Ogawa and Ito[55] reported a novel glycosidation of thioglycosides with sulfenate esters in the presence of TMSOTf (Scheme 13). As a new trend, Sinaÿ et al.[56] and Balavoine et al.[57] independently developed electrochemical glycosylation methods of phenyl thioglycosides via a radical cation generated by electrochemical oxidation. In relation to the above concept, the glycosylation by TBPA, which is a one-electron-transfer homogeneous reagent, was

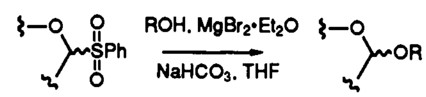
Scheme 14



Scheme 15



Scheme 16



very recently demonstrated by Sinaÿ et al.[58] (Scheme 14). Further, the use of phenyl sulfoxide sugar as a new glycosyl donor in the presence of Tf_2O was demonstrated by Kahne et al.[59] (Scheme 15). On the other hand, Ley and his collaborators[60] developed a glycosylation method using phenyl sulfone as a new anomeric functional group in the presence of $MgBr_2$·Et_2O and $NaHCO_3$ (Scheme 16).

IV. 1-O-Acyl Sugar

An advantage of the 1-*O*-acylated glycosyl donor in the glycosylation method (Table 6) is undoubtedly the easiness of its preparation. The most representative anomeric functional group in this area is the acetyl group. Since Helferich et al.[61] developed the glycosidation of 1-*O*-acetyl sugar with phenol in the presence of TsOH or $ZnCl_2$, several Lewis acids have appeared as effective promoters in the glycosylation, for instance $SnCl_4$ (Lemieux,[62] Hanessian et al.[63]), $FeCl_3$ (Kiso and Anderson,[64a] Lerner[64b]), BF_3·Et_2O (Magnusson et al.),[65] TMSOTf (Ogawa et al.),[66] and $TrClO_4$ (Mukaiyama et al.).[67] The TMSOTf activator was applied to Scharf's synthesis of the disaccharide moiety in avermectins[68] (Scheme 17), and BF_3·Et_2O was used in Gurjar's synthetic studies of the glycopeptidolipid antigen[69] (Scheme 18). $TrClO_4$ was also employed for activation of the 1-*O*-bromoacetyl group.[67] Mukaiyama and his co-workers also introduced the combinational use of $SnCl_4$–$Sn(OTf)_2$,[70] $SnCl_4$–$AgClO_4$,[71] or $GaCl_3$–$AgClO_4$[72] and found that catalytic use of these promoters was good enough to perform the glycosylation reactions of the 1-*O*-acetyl sugar with trimethylsilylated alcohol. Thus, 1,2-*cis*-α-glucosides and -α-ribosides were predominantly obtained from 1-*O*-acetylglucoses and -riboses, respectively, both of which had a nonparticipating group. K-10 montmorillonite[73] was recently used as a new inexpensive catalyst in the glycosylation of a simple alcohol such as methanol or benzyl alcohol. On the other hand, other acyl groups, such as the benzoyl and *p*-nitrobenzoyl groups were employed as good anomeric leaving groups and could be activated by $FeCl_3$ (Lerner),[64b] TMSOTf (Terashima et al.),[74] or BF_3·Et_2O (Russo et al.).[75] Terashima and his co-workers used the 1-*O*-(*p*-nitrobenzoyl)glycosyl donor and TMSOTf with their anthracycline antibiotics synthesis[74] (Scheme 19) while Scharf and collaborators[76] applied Terashima's method to their synthetic studies of everninomicin antibiotics (Scheme 20). Along this line, Charette et al.[77] reported that the catalytic use of TMSOTf promoted the glycosidation of 1-*O*-benzoyl sugar with the trimethylsilyl ether of alcohol. Very recently, Kobayashi et al.[78] introduced a novel glycosyl donor, glycosyl 2-pyridinecarboxylate, which could be activated by $Cu(OTf)_2$ in Et_2O or $Sn(OTf)_2$ in MeCN to predominantly produce the corresponding α- or β-gluco-

Scheme 17

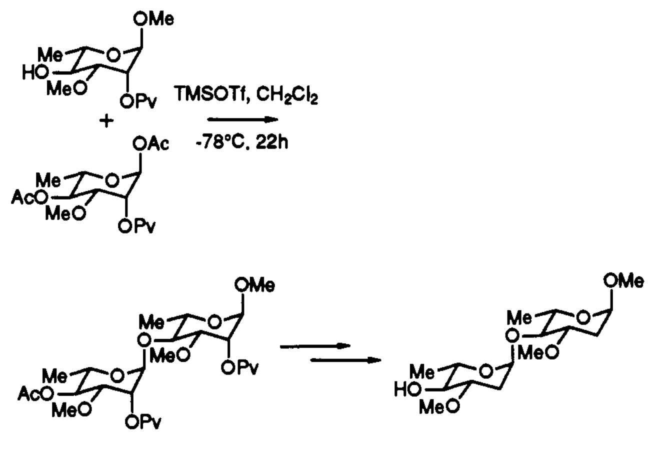
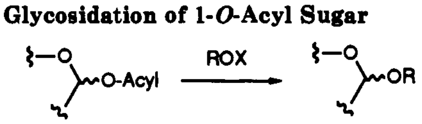
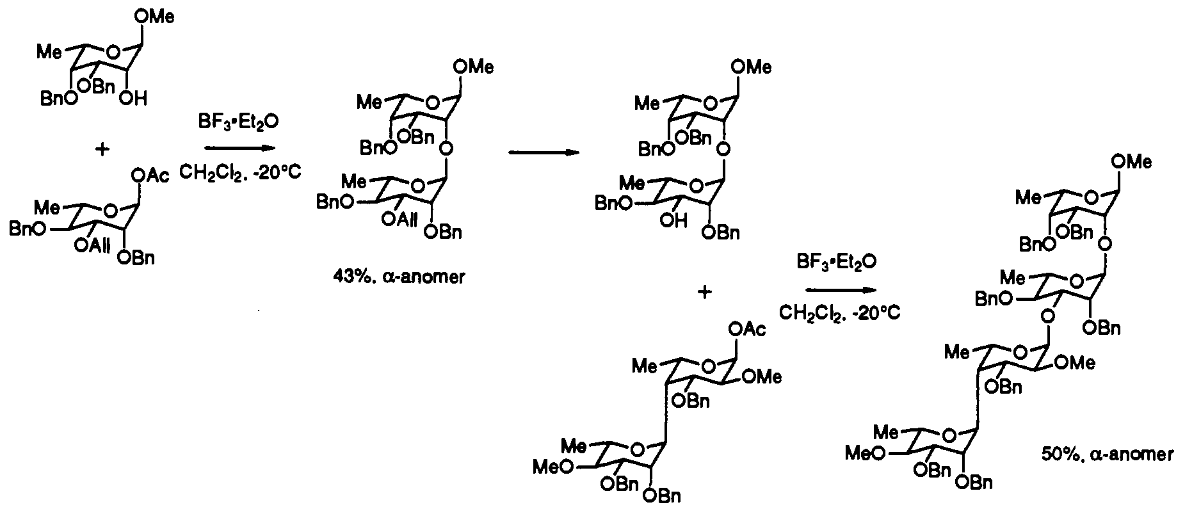


Table 6. Glycosidation of 1-*O*-Acyl Sugar

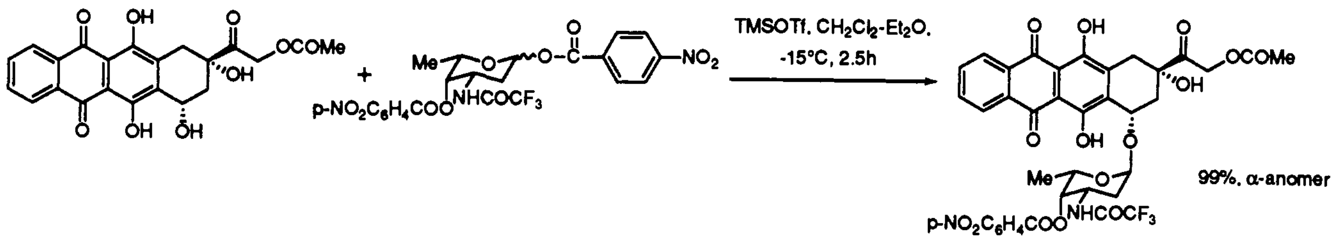


acyl	activator	X	ref(s)
Ac	TsOH or $ZnCl_2$	H	61
	$SnCl_4$	H	62, 63
	$FeCl_3$	H	64
	BF_3·Et_2O	H	65
	TMSOTf	H	66
	$TrClO_4$	H	67
	$SnCl_4$–$Sn(OTf)_2$ (cat.)	TMS	70
	$SnCl_4$–$AgClO_4$ (cat.)	TMS	71
	$GaCl_3$–$AgClO_4$ (cat.)	TMS	72
	K-10 montmorillonite	H	73
$COCH_2Br$	$TrClO_4$	H	67
Bz	$FeCl_3$	H	64b
	TMSOTf (cat.)	TMS	77
COC_6H_4-*p*-NO_2	TMSOTf	H	74
	BF_3·Et_2O	H	75
COPy	$Cu(OTf)_2$ or $Sn(OTf)_2$	H	78

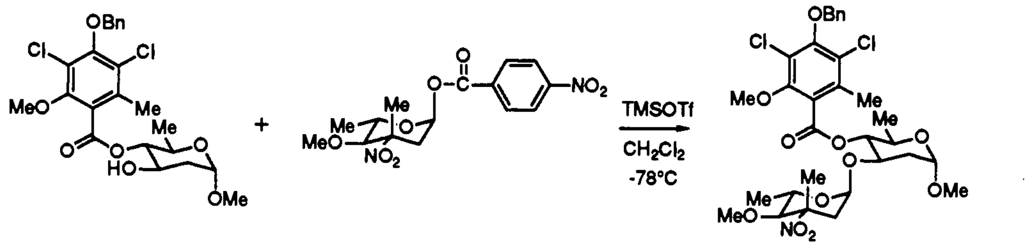
Scheme 18



Scheme 19



Scheme 20

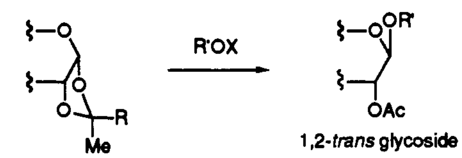


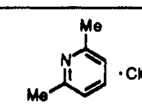
side, respectively. The 2-pyridinecarboxylate group design was based on the remote activation concept which was originally defined by Hanessian.[33]

V. Ortho Ester

The ortho ester method, in particular, has been widely studied by Kochetkov and co-workers and employed for construction of 1,2-*trans*-glycosidic linkages (Table 7). A *tert*-butyl ortho ester first appeared as a glycosyl donor with 2,6-dimethylpyridinium perchlorate as the best promoter.[79] To eliminate their disadvantages, the modified 1,2-*O*-(1-cyanoethylidene) derivatives were prepared from the corresponding glycosyl halides by treatment with KCN in the presence of n-Bu_4NBr in CH_3CN and used in the glycosylation of the trityl ethers of the alcohols. Several glycosylation promoters of the 1,2-*O*-(1-cyanoethylidene) group were introduced, for instance $TrBF_4$ (Kochetkov et al.),[80] $TrClO_4$ (Kochetkov et al.),[81] and AgOTf (Kochetkov et al.).[82] Also, the 1,2-*O*-[1-[(*p*-methylphenyl)thio]ethylidene] group was employed in the ortho ester glycosylation method. This functional group was effectively activated by $TrClO_4$ (Kochetkov et al.)[83] and NIS–TfOH (van Boom et al.).[84]

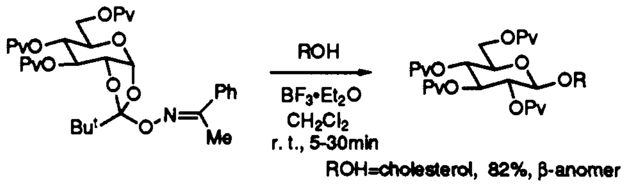
Table 7. Glycosidation of Ortho Ester



R	activator	X	ref
O-^{t}Bu		Tr	79
CN	$TrBF_4$ (cat.)	Tr	80
	$TrClO_4$ (cat.)	Tr	81
	AgOTf (cat.)	Tr	82
SEt, S-C_6H_4-*p*-Me	$TrClO_4$ (cat.)	Tr	83
	NIS–TfOH	H	84

In the case of NIS–TfOH, it was not necessary to protect the glycosyl donor with a trityl group. On the other hand, Kunz et al.[85] recently reported a new glycosylation method using a new glycosyl donor, 1,2-*O*-[1-[[*N*-(1-phenylethylidene)amino]oxyl]-2,2-dimethylpropylidene] glucopyranoside, in the presence of BF_3·Et_2O in CH_2Cl_2 (Scheme 21).

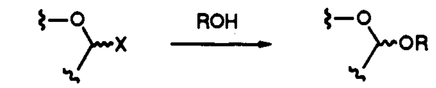
Scheme 21



VI. 1-O- and S-Carbonate

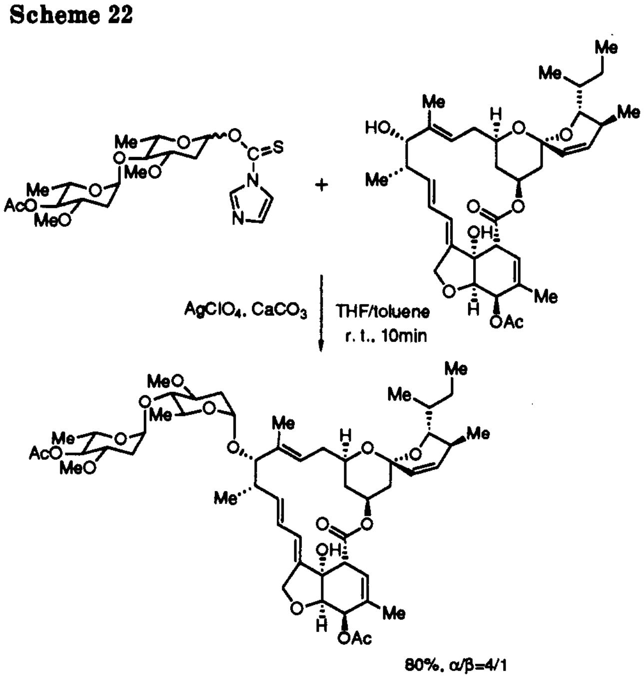
Some representative methods are summarized in Table 8. Since Pougny[86] developed the glycosylations using 1-O-xanthate glycosyl donors in the presence of $BF_3{\cdot}Et_2O$, Ley and his collaborators have extensively studied the use of imidazole carbonate derivatives[87] and imidazolethiocarbonates[88] in the glycosylation reaction. The former glycosyl donor was effectively activated by $ZnBr_2$ and the latter one was promoted by $AgClO_4$. The latter combination was effectively applied to their total synthesis of avermectin B_{1a}[88] (Scheme 22). On the other hand, Sinaÿ and co-workers[89] recently introduced an anomeric S-xanthate as a leaving group of the glycosyl donor with $Cu(OTf)_2$ or DMTST as its effective promoter. MeSOTf was also used by Lönn et al. for the effective glycosylation of sialic acid[90] and applied it to their GM_3 ganglioside synthesis[90c] (Scheme 23). Very recently, the use of glycosyl 1-piperidinecarbodithioates by activation of MeOTf or AgOTf in CH_2Cl_2 was also introduced by Fügedi et al.[91] Before these glycosylation methods, Mukaiyama et al.[92] developed a glycosylation by the successive treatment of 1,2-cyclic thiocarbonate with $MeOSO_2F$ and alcohol in the presence of CsF (Scheme 24).

Table 8. Glycosidation of 1-O- and S-Carbonate

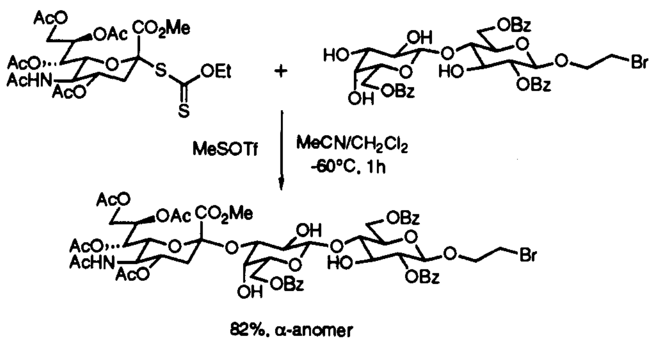


X	activator	ref
—O–C(=S)–SMe	$BF_3{\cdot}Et_2O$	86
—O–C(=O)–N(imidazolyl)	$ZnBr_2$	87
—O–C(=S)–N(imidazolyl)	$AgClO_4$	88
—S–C(=S)–OEt	$Cu(OTf)_2$	89
	DMTST	89
	MeSOTf	90
—S–C(=S)–N(piperidinyl)	AgOTf or MeOTf	91

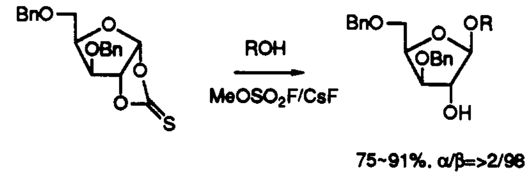
Scheme 22



Scheme 23



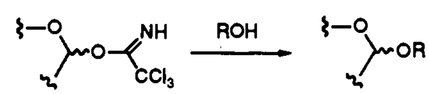
Scheme 24



VII. Trichloroimidate

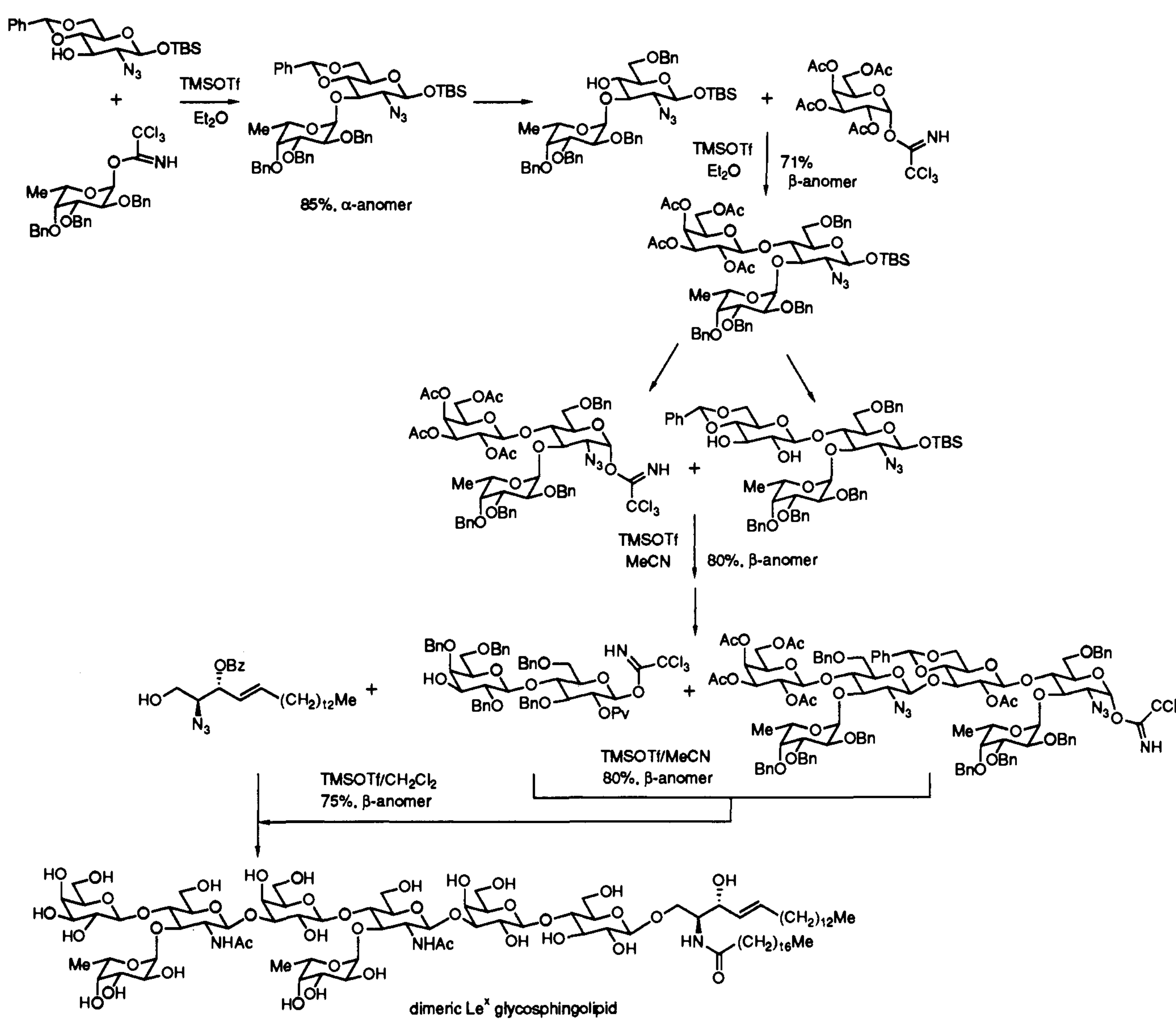
Trichloroimidate-mediated glycosylation was announced by Schmidt and his co-workers[93] in 1980 as an alternative useful method to the classical Koenigs–Knorr procedure and now appears to be one of the most ideal glycosylation protocol (Table 9). Further, this method was very well reviewed in his own articles.[2g,j,l] Although the initial use of an imidate as a glycosyl donor was reported by Sinaÿ in 1976,[94] the Schmidt's glycosylation method excels in many points. The thermally and chemically stable trichloroimidate glycosyl donor was easily synthesized from the corresponding 1-hydroxyl sugar by treatment of trichloroacetonitrile in the presence of a base such as K_2CO_3, NaH, or DBU. The glycosylation reaction was smoothly promoted by catalytic use of $BF_3{\cdot}Et_2O$,[93] TMSOTf,[2g] or CCl_3CHO[95] under mild conditions. Another Lewis acid, PPTS, was also used as an effective activator by Nicolaou et al.[96] Recently, Urban and co-workers[97] investigated a new preparation of the trichloroimidate using cesium carbonate as a base and the novel promoter, $ZnBr_2$, for the

Table 9. Glycosidation of Trichloroimidate

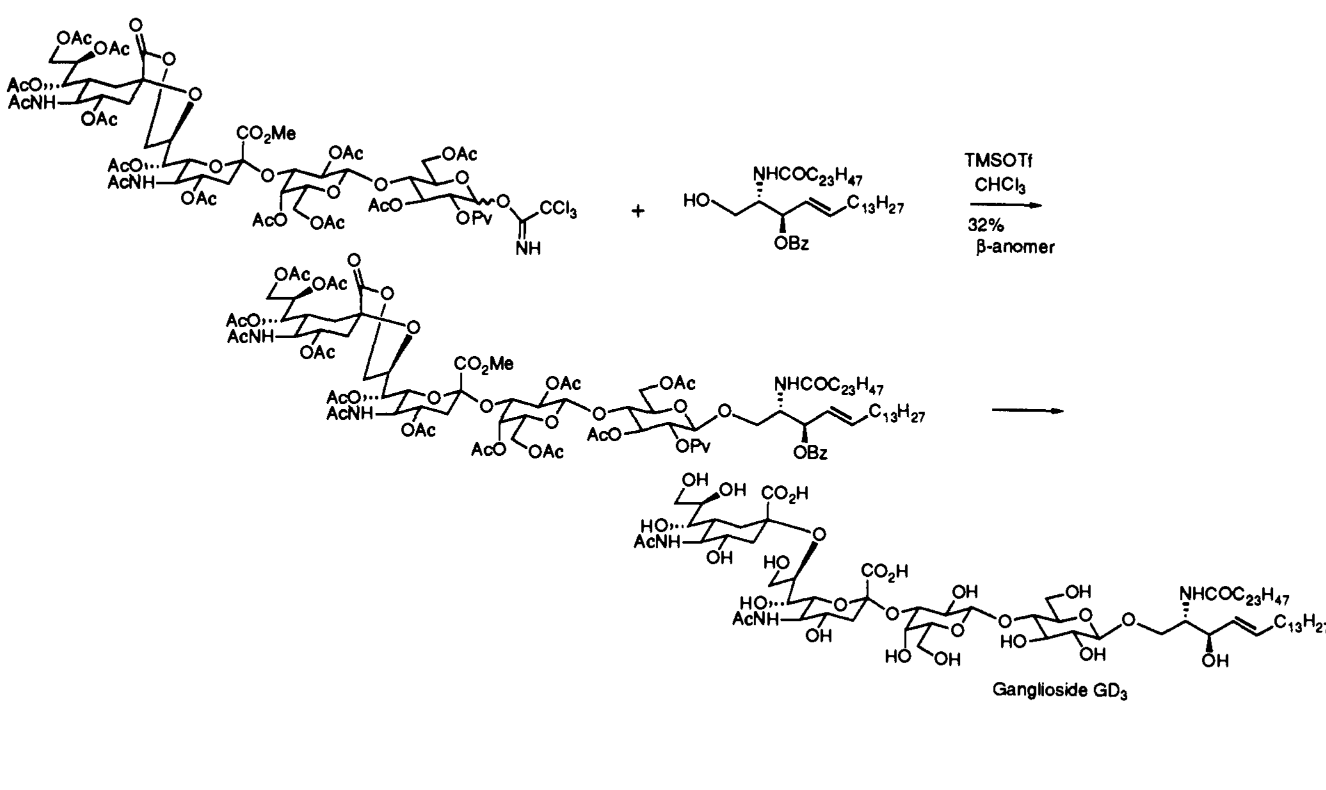


activator	ref	activator	ref
$BF_3{\cdot}Et_2O$	93a	PPTS	96
TMSOTf	2g	$ZnBr_2$	97
CCl_3CHO	95		

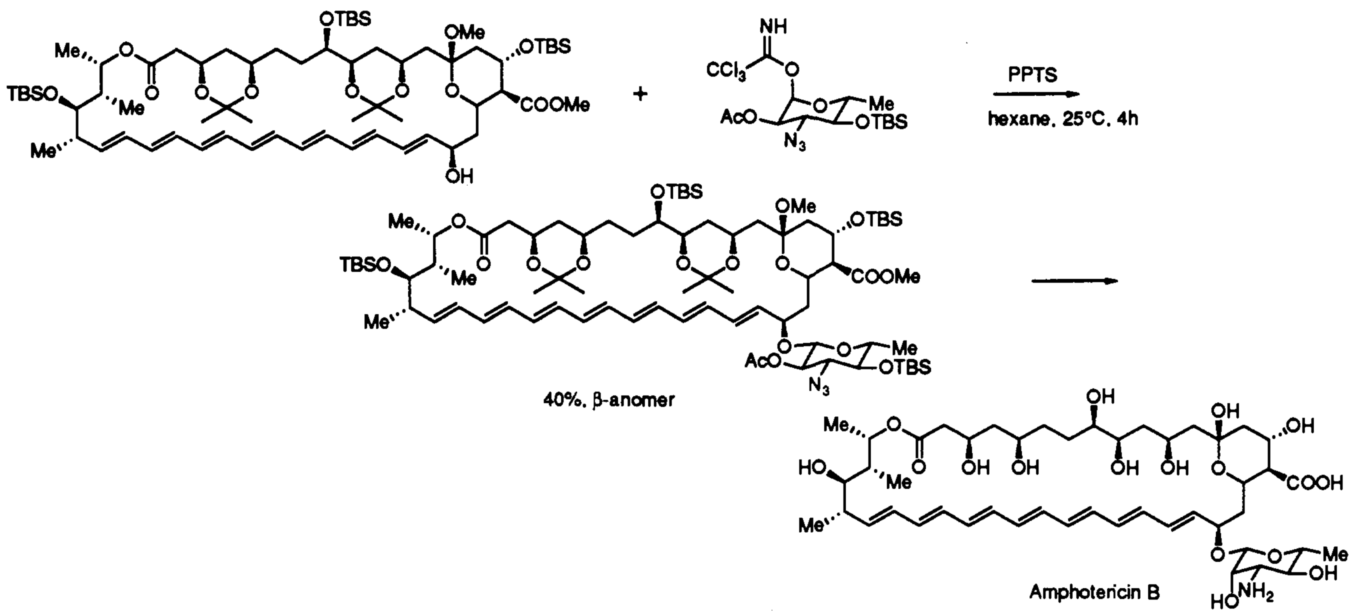
Scheme 25



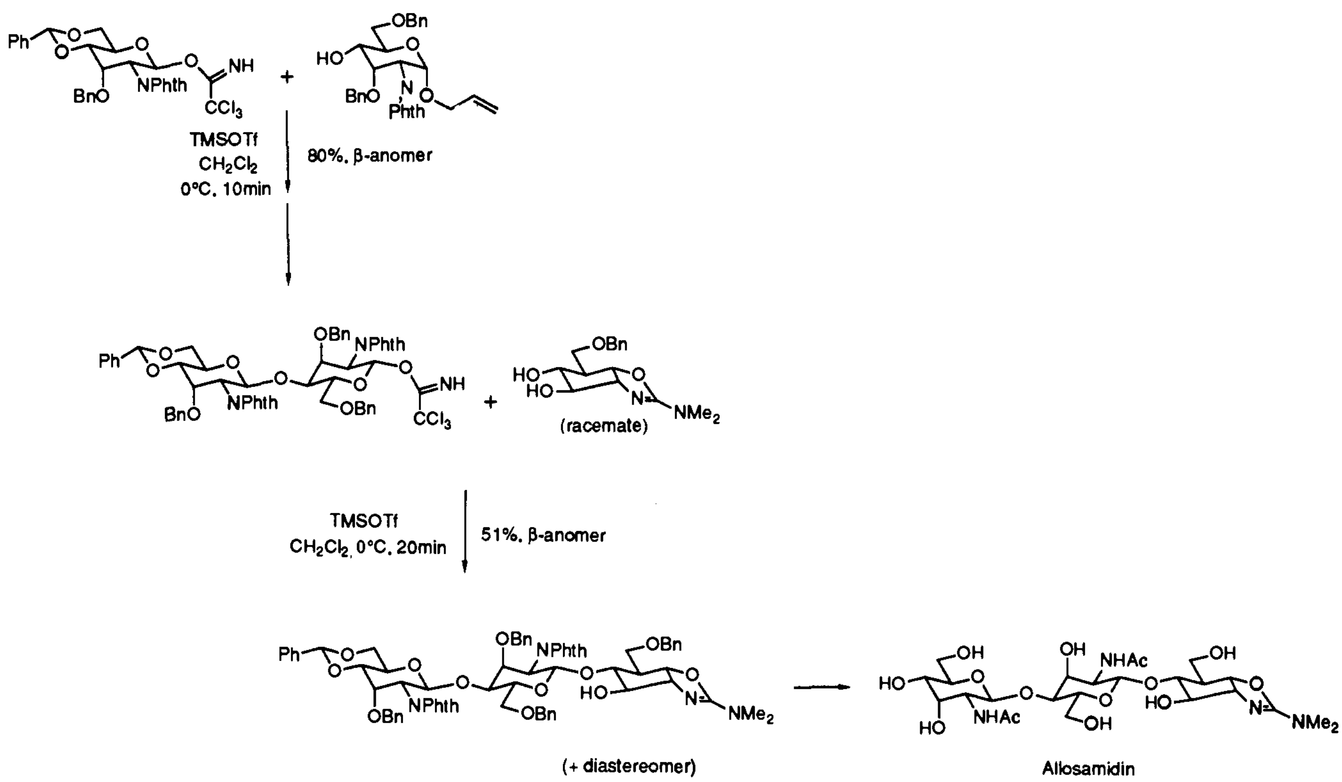
Scheme 26



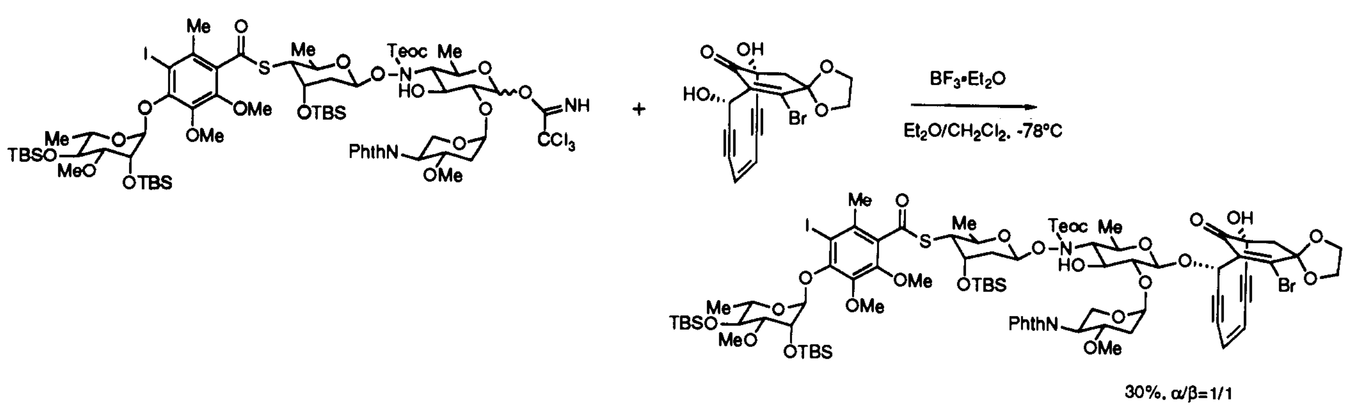
Scheme 27



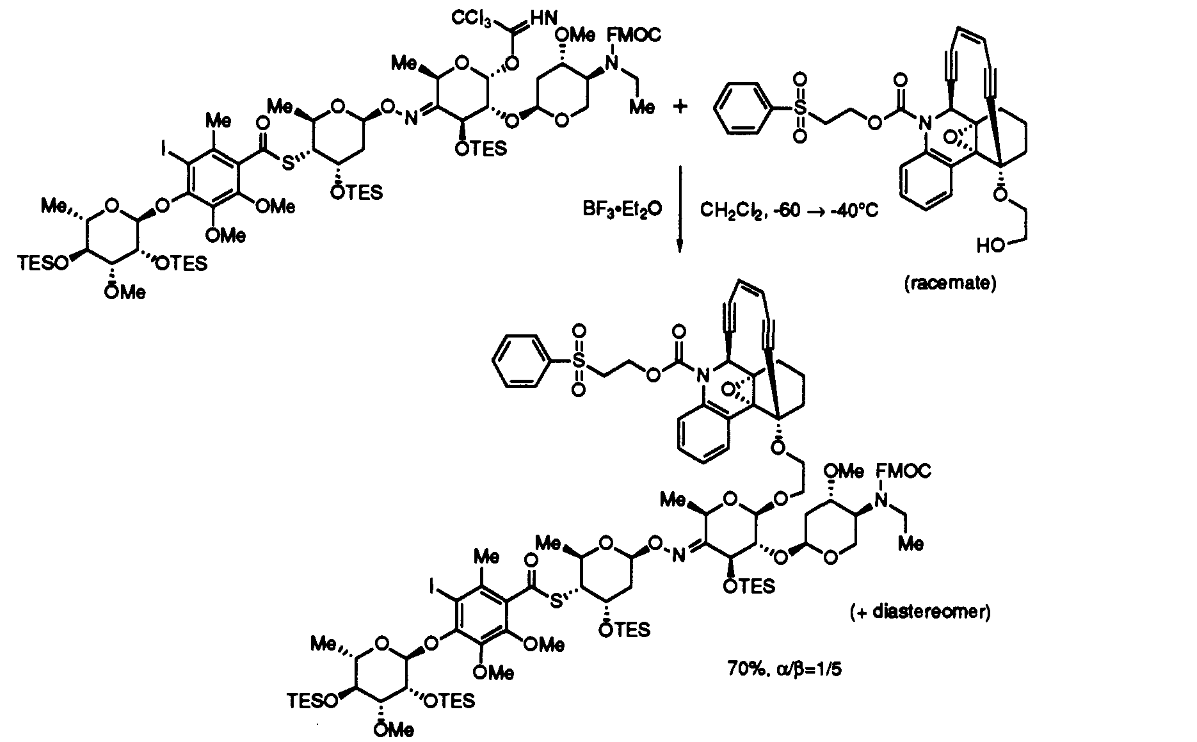
Scheme 28



Scheme 29



Scheme 30

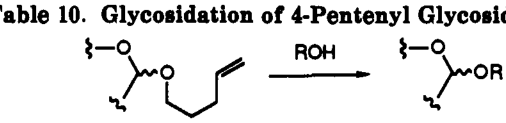


Schmidt's glycosylation. Up to now, the trichloroimidate method has been found to have wide applications in the synthesis of natural products, for instance Schmidt's glycosphingolipids syntheses[98] (Scheme 25), Ogawa's gangliosides syntheses[99] (Scheme 26), Nicolaou's amphotericin B synthesis[96] (Scheme 27), Vasella's allosamidin synthesis[100] (Scheme 28) and Barrett's bulgecin C synthesis.[101] Very recently, Danishefsky et al.[102] and Nicolaou et al.[103] also effectively applied this glycosylation protocol to their synthetic studies of enediyne antibiotics, calicheamicin (Scheme 29), and its hybrid molecule (Scheme 30).

VIII. 4-Pentenyl Glycoside

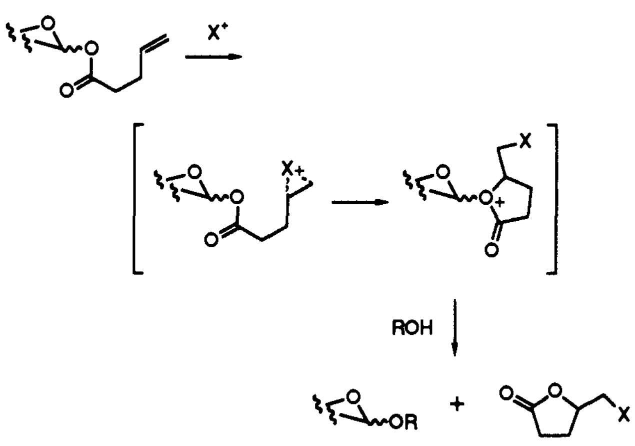
Fraser-Reid and his co-workers introduced a 4-pentenyl group as a new and effective leaving group at the anomeric center of the glycosyl donor in 1988.[104] The 4-pentenyl group was originally used as the only protective group of the 1-hydroxyl group of the sugar and it was found to be selectively deprotected by hydrolysis using NBS in CH_3CN–H_2O.[105] However, they found that when an alcohol was employed instead of water during the deprotection reaction conditions, the corresponding *O*-glycoside was exclusively formed. The 4-pentenyl glycosides were usually prepared as a mixture of α- and β-anomers by the reactions of 1-hydroxyl sugars and 4-pentenyl alcohol in the presence of an acid catalyst. Their glycosylation reactions were promoted by IDCP[104,106] or more the reactive NIS–TfOH[107] or NIS–Et_3SiOTf[108] (Table 10). In these glycosylation studies, Fraser-Reid and his collaborators found a quite attractive and new concept in this area, "armed and disarmed sugar" [106a,107b,108] which will be discussed later in detail in this review (see section VXII.A). Very recently, Kunz et al.[109] and Fraser-Reid et al.[10] independently reported along these lines the use of 4-pentenyl esters as glycosyl donors (Scheme 31).

Table 10. Glycosidation of 4-Pentenyl Glycoside



activator	ref(s)
IDCP	104, 106
NIS–TfOH	107
NIS–Et_3SiOTf	108

Scheme 31



IX. Phosphate Derivatives

Several glycosyl donors possessing a phosphorus atom in the leaving group at the anomeric center have also been investigated (Table 11). Since phosphorus compounds can be easily modified by several kinds of other atoms, a wide variety of leaving groups with different properties can be designed. Hashimoto and Ikegami introduced glycosyl diphenyl phosphates,[111] glycosyl diphenylphosphineimidates,[112] and glycosyl phosphoroamidates[113] in this field. These glycosyl donors were effectively activated by TMSOTf or BF_3·Et_2O to

Scheme 32

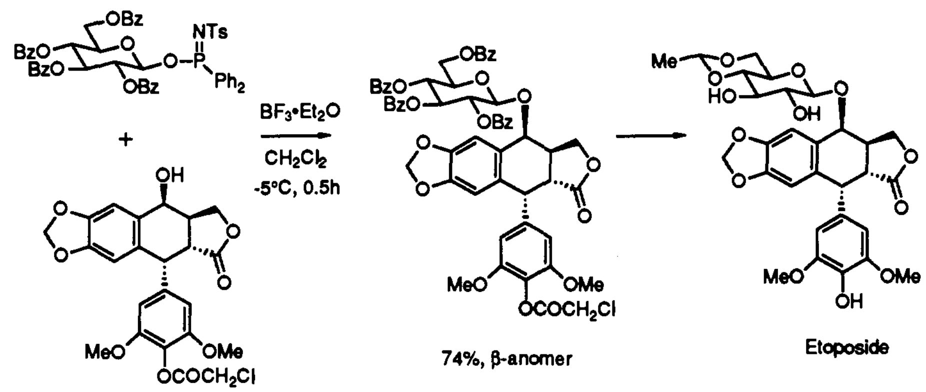
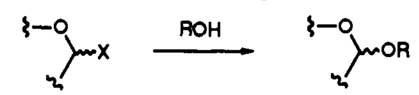


Table 11. Glycosidation of Phosphate Derivative



X	activator	ref
—O—P(=O)—(OPh)$_2$	TMSOTf	111
—O—P(=NTs)—Ph$_2$	TMSOTf $BF_3{\cdot}Et_2O$	112
—S—P(=NPh)—(NMe$_2$)$_2$	LPTS–Bu$_4$NI	114
—O—P(=O)—(NMe$_2$)$_2$	$BF_3{\cdot}Et_2O$ TMSOTf	113
—O—P(=S)—Me$_2$	$AgClO_4$ $TrClO_4$–I_2 $TrClO_4$	115a 115b 115c

predominantly afford 1,2-*trans*-β-linked glycosides even in the case of benzyl-protected glycosyl donors. Further, they found that S-glycosyl phosphorodiamidimidothioates[114] was promoted by LPTS–Bu$_4$NI to selectively give 1,2-*cis*-glycosidic linkages. The diphenylphosphineimidate method was applied to the glycosylation of podophyllotoxin (Scheme 32).[112c] On the other hand, Inazu and his co-workers[115] developed several types of dimethylphosphinothioate as quite stable glycosyl donors and found that these were smoothly glycosidated by $AgClO_4$,[115a] I_2–$TrClO_4$,[115b] or $TrClO_4$[115c] in benzene.

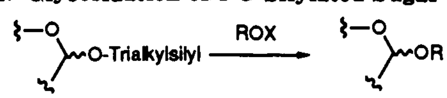
X. 1-O-Sulfonyl Glycoside

The use of 1-O-sulfonyl derivatives as a glycosyl donor produced major advantages in 1970–1980.[2c,g] Especially, the 1-O-toluenesulfonyl group was widely studied by Schuerch's group.[116] However, unfortunately, only few significant advances have appeared in this field since 1980 except for the β-D-mannoside synthesis by Schuerch et al. (see section XVI.B).

XI. 1-O-Silylated Glycoside

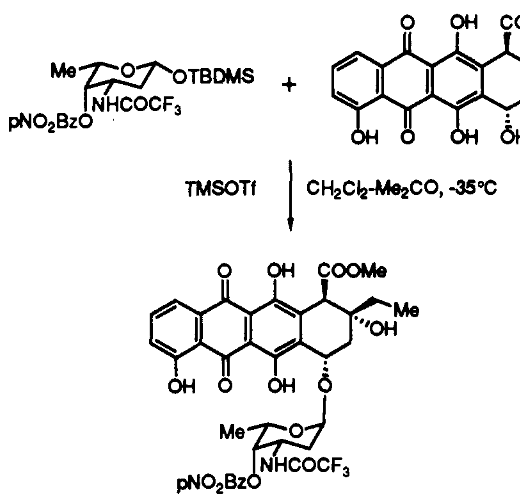
In the employment of 1-O-silylated glycoside as a glycosyl donor, trimethylsilyl and *tert*-butyldimethylsilyl groups were preferentially used (Table 12). Tietze and his co-workers[117] introduced a new glycosylation reaction of 1-O-trimethylsilyl glycoside with phenyltrimethylsilyl ethers in the presence of a catalytic amount of TMSOTf as a Lewis acid and Glaudemans et al.[118] modified the method for the formation of the (1 → 6)-oligosaccharide linkage using a 6-O-*tert*-butyldimethylsilyl-protected glycosyl acceptor. Cai and his co-workers[119] also developed a method for the synthesis of alkyl O-glycoside from 1-O-trimethylsilyl glycoside by the activation by $BF_3{\cdot}Et_2O$ instead of TMSOTf. On the other hand, the 1-O-*tert*-butyldimethylsilyl glycosyl donor was used for the synthesis of 2-deoxy glycosides by Priebe et al.[120] and was also employed in the anthracycline oligosaccharide synthesis by Kolar et al.[121] (Scheme 33) Mukaiyama and his co-workers[122] very recently developed stereoselective glycosylation reactions of 1-O-trimethylsilyl sugars. Thus, 1,2-*trans*-ribofuranosides were predominantly synthesized by the glycosidation of 1-O-trimethylsilyl ribofuranose and trimethylsilyl ethers in the presence of a catalytic amount of TMSOTf and $Ph_2Sn{=}S$ as an additive while 1,2-*cis*-ribofuranosides and 1,2-*cis*-glucopyranosides were selectively prepared by the addition of $LiClO_4$ in the above reaction conditions.

Table 12. Glycosidation of 1-O-Silylated Sugar



trialkylsilyl	activator	X	ref(s)
TMS	TMSOTf (cat.)	TMS	117, 118
	$BF_3{\cdot}Et_2O$	H	119
	TMSOTf (cat.)–$Ph_2Sn{=}S$	TMS	122
TBS	TMSOTf	H	120, 121

Scheme 33

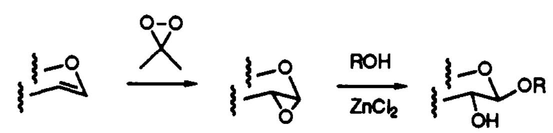


82%, α-anomer

XII. 1,2-Anhydro Sugar

Since the first 1,2-anhydro sugar, that is, Brigl's anhydride[123] was reported in 1922, several uses of the 1,2-anhydro sugar for the disaccharide synthesis were investigated.[2g] However, few significant advances appeared in practical means until Danishefsky's recent studies[124] in 1989. Danishefsky and his co-workers developed a convenient method for the direct preparation of the 1,2-anhydro sugar from glycal using dimethyldioxirane as an effective epoxidation reagent. They also investigated the wide use of the 1,2-anhydro sugar for the synthesis of several types of glycosides including glycosyl fluoride, thioglycoside, and so on. The 1,2-anhydro sugar was smoothly coupled with alcohol in the presence of $ZnCl_2$ in THF under mild conditions to exclusively give the 1,2-*trans*-glycoside (Scheme 34).

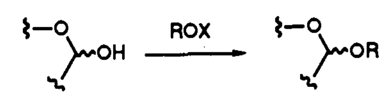
Scheme 34

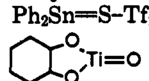


XIII. 1-Hydroxyl Sugar

The direct formation of a glycosidic bond from the 1-hydroxyl sugar has undoubtedly high efficiency in the glycosylation method (Table 13). The initial[125] and several recently modified[126] Fischer–Helferich methods using an acid catalyst are now useful for obtaining simple glycosides such as methyl, benzyl, allyl, and simple thioglycosides which are widely used as chiral synthones.[21] The team led by Koto, Morishima, and Zen[127] developed a glycosidation of the 1-hydroxyl sugar via glycosyl bromide as an intermediate using methanesulfonic acid, cobalt(II) bromide, and tetraethylammonium perchlorate or tetrabutylammonium bromide. A one-stage approach via 1-*O*-sulfonyl glycoside by the treatment of 1-hydroxyl sugar with a mixture of *p*-nitrobenzenesulfonyl chloride, AgOTf, $AcNMe_2$ and Et_3N was also introduced by them.[128] Along this line, Szeja[129] reported the glycosylation by TsCl under phase-transfer conditions. On the other hand, the anomeric *O*-alkylation method was announced by Schmidt et al. in 1979.[2g,l,130] The 1-hydroxyl sugar was generally activated by *t*-BuOK or NaH and then coupled with alkyl triflate. In the case of the secondary alkyl triflate as a glycosyl accepter, aprotic dipolar solvents, HMPT–DMF or HMPT–THF were effective for their glycosylations.[130h] In relation to this glycosylation study, the glycosidation of partially *O*-unprotected sugars with decyl triflate were interestingly investigated.[130g] On the other hand, the practical application of the Mitsunobu reaction for the synthesis of an aryl glycoside from the 1-hydroxyl sugar was recently demonstrated by Roush's group.[131] Very recently, Mukaiyama and his co-workers developed an elegant method for the stereoselective direct syntheses of both 1,2-*cis*- and *trans*-ribofuranosides from 1-hydroxylribofuranoses and alcohols or trimethylsilylated ethers by the combinational uses of diphosphonium salts–$^iPr_2NEt$,[132] [1,2-benzenediolato(2-)-*O*,*O'*]oxotitanium–Tf_2O–$^iPr_2NEt$,[133] or diphenyl sulfide–Tf_2O–CsF with or without lithium perchlorate.[134]

Table 13. Glycosidation of 1-Hydroxyl Sugar

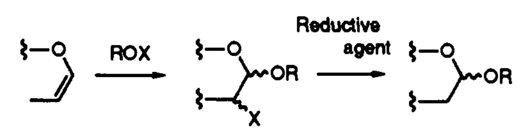


activator	X	ref
MsOH–$CoBr_2$–R'_4NBrX (R' = Et, Bu; X = Br, ClO_4)	H	127
p-$NO_2C_6H_4SO_2Cl$–AgOTf–Et_3N–$AcNMe_2$	H	128
^tBuOK or NaH	Tf or H	130
DEAD–Ph_3P	H (R = aryl)	131
$^nBu_3P$=O–Tf_2O–$^iPr_2NEt$	H or TMS	132
Ph_2Sn=S–Tf_2O–CsF	H or TMS	134
 -Tf_2O-CsF-$^iPr_2NEt$	TMS	133

XIV. Glycal

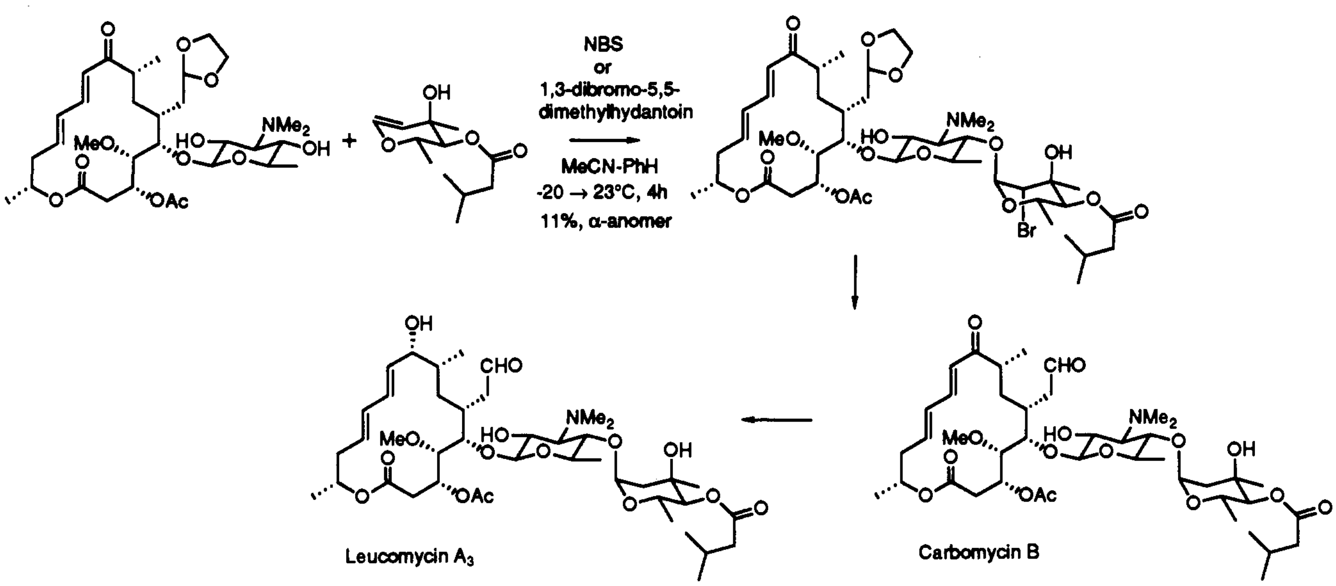
Glycal is a very versatile synthetic intermediate especially in the synthesis of 2-deoxy glycoside. Since Lemieux and his co-workers[135] investigated that the reaction of glycal and simple alcohol in the presence of I_2, Ag salt, and base gave 2-deoxy-2-iodoglycoside in good yield, several more practical promoters, IDCP (Lemieux et al.,[136] Danishefsky et al.[137]), NBS (Tatsuta et al.),[138] and NIS (Thiem et al.),[139] were introduced (Table 14). The preferentially obtained 2-deoxy-2-halo-α-glycoside by these promoters was easily converted into the desired 2-deoxy-α-glycoside by reductive dehalogenation. Thus, Tatsuta's method was effectively applied to his first total synthesis of carbomycin B, leucomycin A_3[140] (Scheme 35) and tylosin[141] and Kinoshita–Toshima–Tatsuta's total synthesis of elaiophylin (azalomycin B)[142] (Scheme 36). Thiem's procedure also found wide application, for instance in his kijanimicin oligosaccharides synthesis[143] (Scheme 37), Horton's anthracycline glycoside synthesis[144] (Scheme 38), Monneret's daunosamine disaccharides synthesis,[145] Danishefsky's avermectin synthesis[146] (Scheme 39), and so on. The first use of IDCP by Lemieux[136] lead to Danishefsky's recent studies of IDCP glycosylation (see section XVII.A).[137] Thiem and Klaffke[147] recently improved the original NIS method by the transformation of an alcohol into the tin–alkoxide to

Table 14. Glycosidation of Glycal

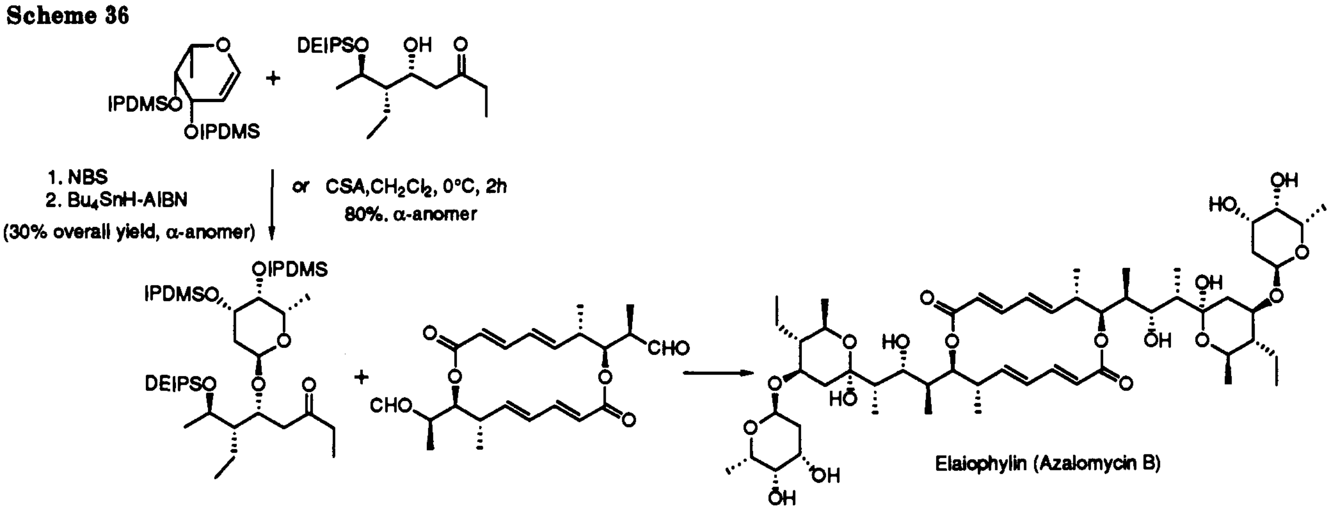


activator	X	ref(s)	reductive agent
IDCP	I	136, 137	H_2–Pd
NBS	Br	138	H_2–Raney-Ni
NIS	I	139	or
PhSeCl	SePh	149	Bu_4SnH–AIBN
CSA	H	153	
TsOH	H	154	
$Ph_3P{\cdot}HBr$	H	155	
AG50 WX2-resin	H	156	

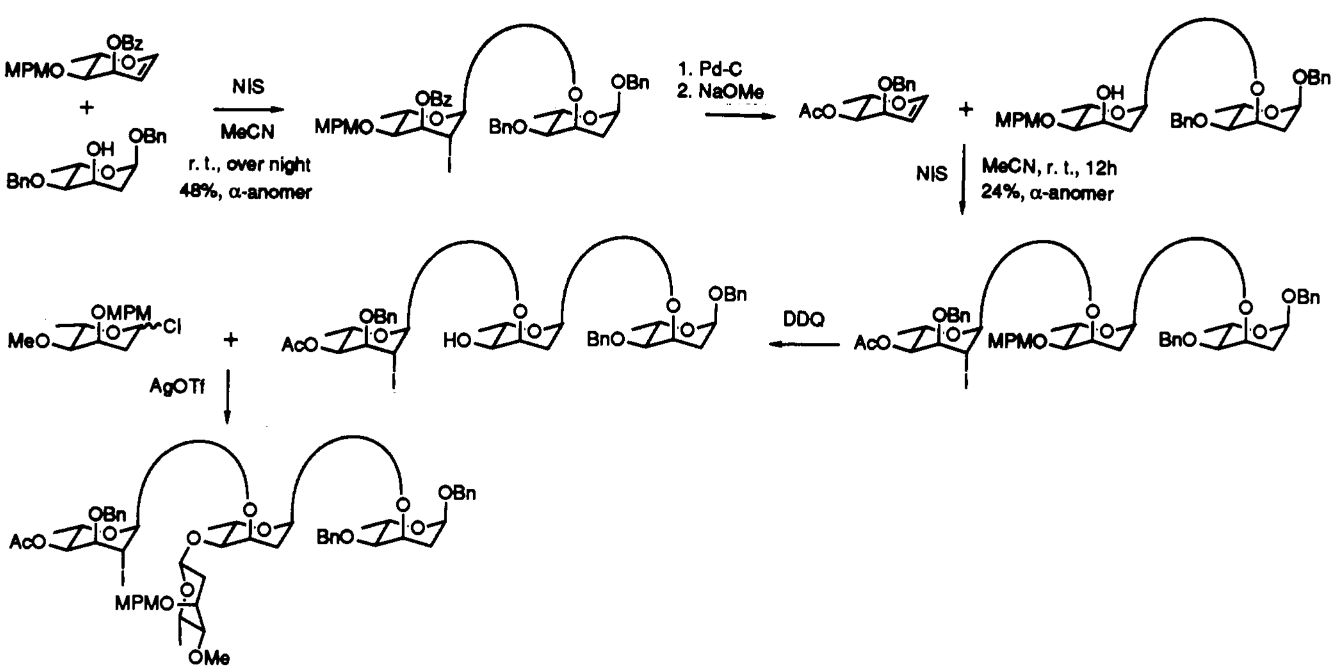
Scheme 35



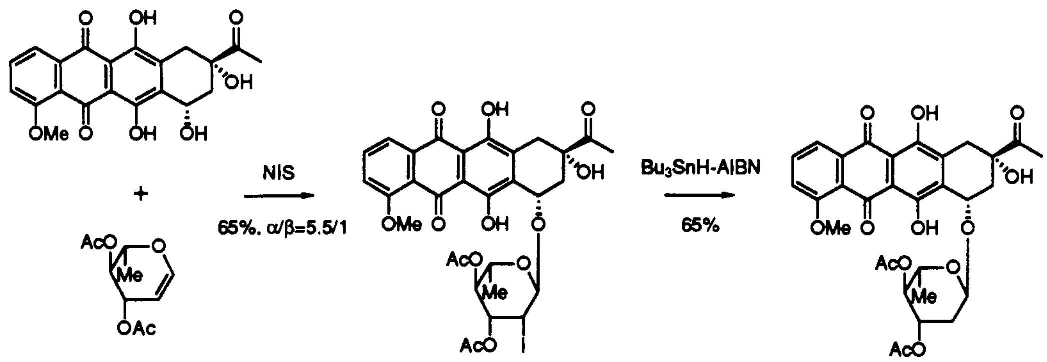
Scheme 36



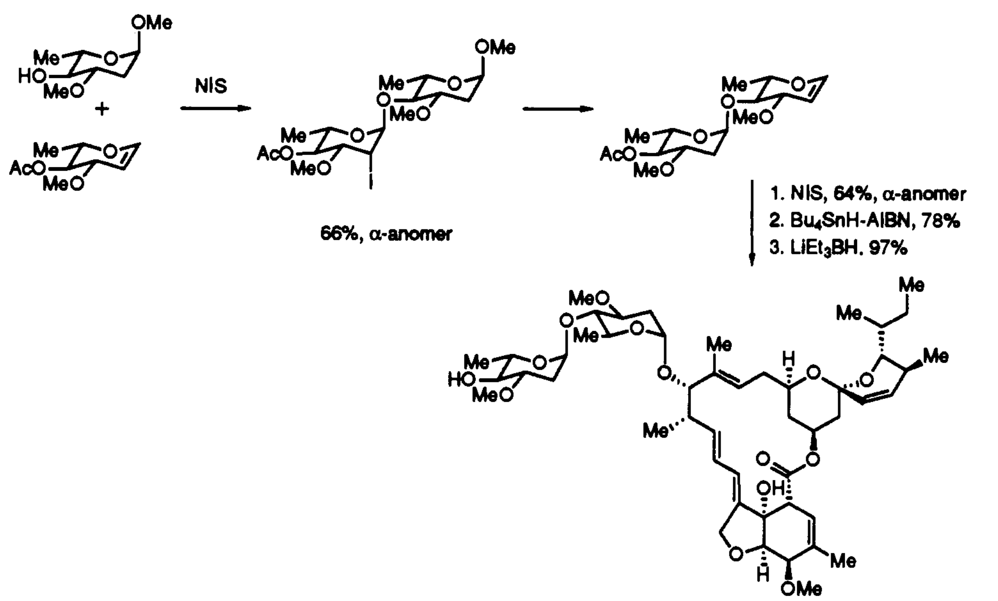
Scheme 37



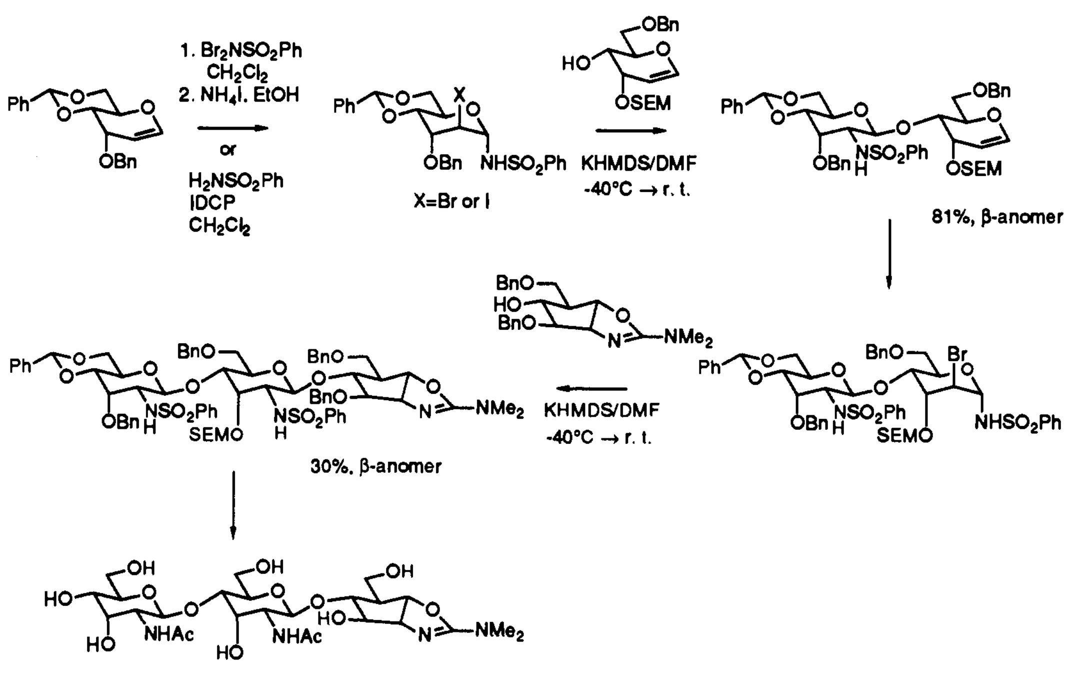
Scheme 38



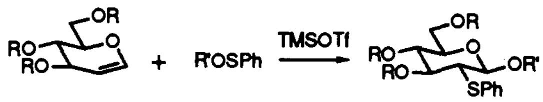
Scheme 39



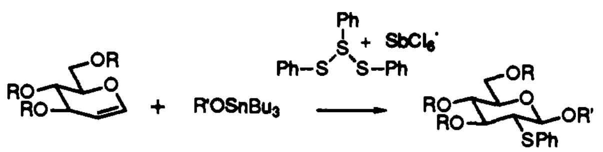
Scheme 40



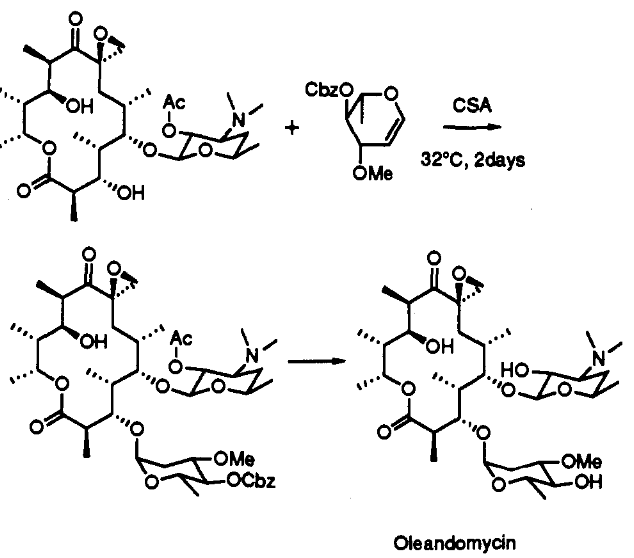
Scheme 41



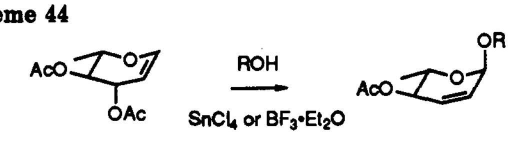
Scheme 42



Scheme 43



Scheme 44

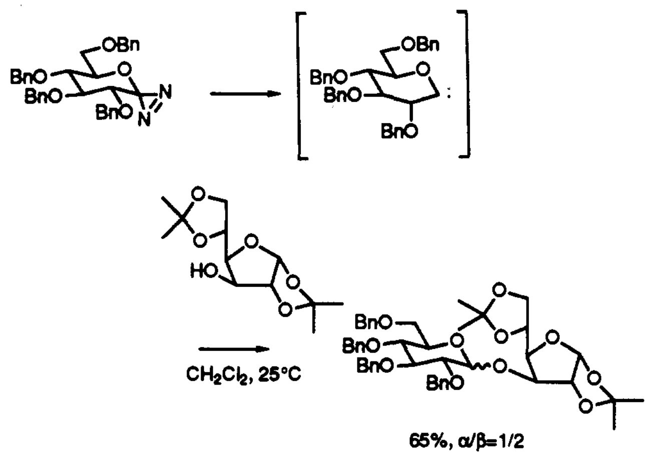


enhance the reactivity of the glycosyl acceptor. Very recently, Danishefsky and his co-workers[148] developed the sulfonamidoglycosylation reaction of glycal by the combinational use of IDCP and benzenesulfonamide or the use of *N,N*-dibromobenzenesulfonamide to effectively prepare the 2-amino-2-deoxy-β-glycosides. This method was elegantly applied to their total synthesis of allosamidin[148b] (Scheme 40). Sinaÿ and his co-workers[149] developed an alternative approach using PhSeCl as a glycosyl activator and this method was used in Barrett's avermectin α-disaccharide synthesis.[150] Recently, the addition of the phenyl sulfenate ester to glycal in the presence of TMSOTf and the electrophilic activation of glycal by phenylbis(phenylthio)sulfonium salt were announced by Ogawa et al.[151] (Scheme 41) and Franck et al.[152] (Scheme 42), respectively. In these glycosylation methods, 2-deoxy-2-(phenylthio)-β-glycosides, which were generally converted into the 2-deoxy-β-glycoside by hydrogenolysis using Raney-Ni as a catalyst, were produced with moderate stereoselectivity. On the other hand, CSA,[153] TsOH,[154] triphenylphosphine hydrobromide,[155] and AG50 WX2-resin[156] appeared in this field to directly obtain the desired 2-deoxy-α-glycoside from glycal. Among them, the glycosylation by CSA was effectively employed in Kinoshita–Toshima–Tatsuta's total synthesis of elaiophylin[153a] (Scheme 36), Tatsuta's total synthesis of oleandomycin[153b] (Scheme 43) and Wakamatsu's synthetic study of elaiophylin.[153c] On the other hand, BF_3·Et_2O[157] and $SnCl_4$[158] were used as glycosylation promoters which afforded the 2,3-unsaturated glycoside resulting from the allylic rearrangement (the Ferrier reaction) of glycal (Scheme 44).

XV. Others

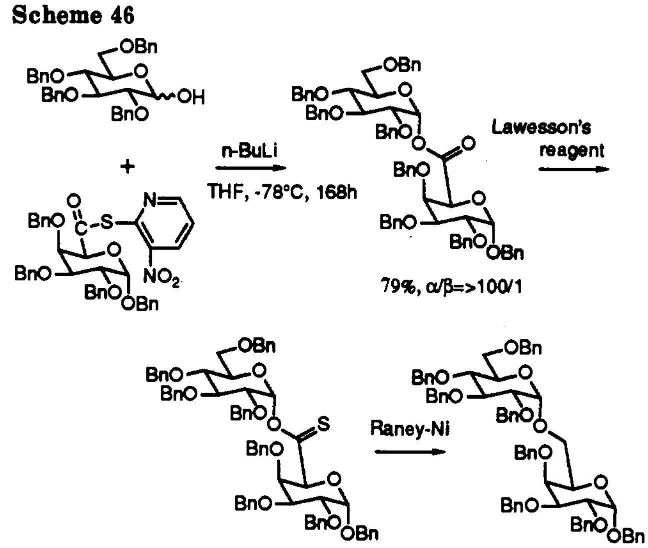
Vasella et al.[159] recently introduced a new approach to glycoside synthesis using the glycosylidene carbene generated from the diazirine sugar as a novel type of glycosyl donor. The glycosylidene carbene reacted with alcohol in the absence of any additive (Scheme 45).

Scheme 45



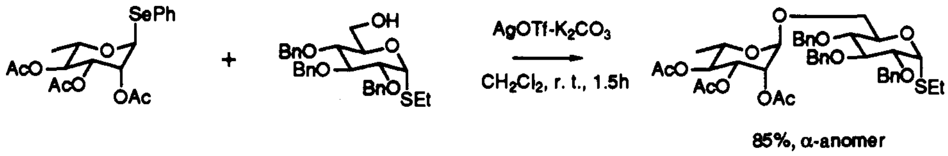
The redox glycosylation via reductive methylation of a thionoester intermediate was reported by Barrett et al.[160] (Scheme 46). The thionoester was prepared by

Scheme 46



esterification of a 1-hydroxyl sugar followed by Lawesson thionation. On the other hand, the use of phenyl selenoglycoside as a new glycosyl donor and its selective activation over ethyl thioglycoside by AgOTf and K_2CO_3 were demonstrated by Pinto et al.[161] (Scheme 47). Further, Noyori and his co-workers reported the photochemical[162] and electrochemical[163] glycosidations

Scheme 47



of *O*-protected and unprotected aryl glycosides as a new trend.

XVI. Special Methods

A. 2-Deoxyglycoside Synthesis

Several types of α- and β-2-deoxyglycosides frequently appear in naturally occurring bioactive substances such as aureolic acid antibiotics, anthracycline antibiotics, cardiac glycosides, avermectins, erythromycins, or recently discovered enediyne antibiotics (Figure 1). However, the efficient glycosidation of 2-deoxy sugar, especially, β-selective glycosidation has been a long-standing problem in this field.[164g] The main reasons why highly stereocontrolled and efficient glycosidation of a 2-deoxy sugar is difficult are the lack of stereodirecting anchimeric assistance from the C-2-position and the low stability of a glycosidic bond of a 2-deoxy sugar in acidic conditions due to the lack of an electron-withdrawing C-2-substituent. Thiem and his

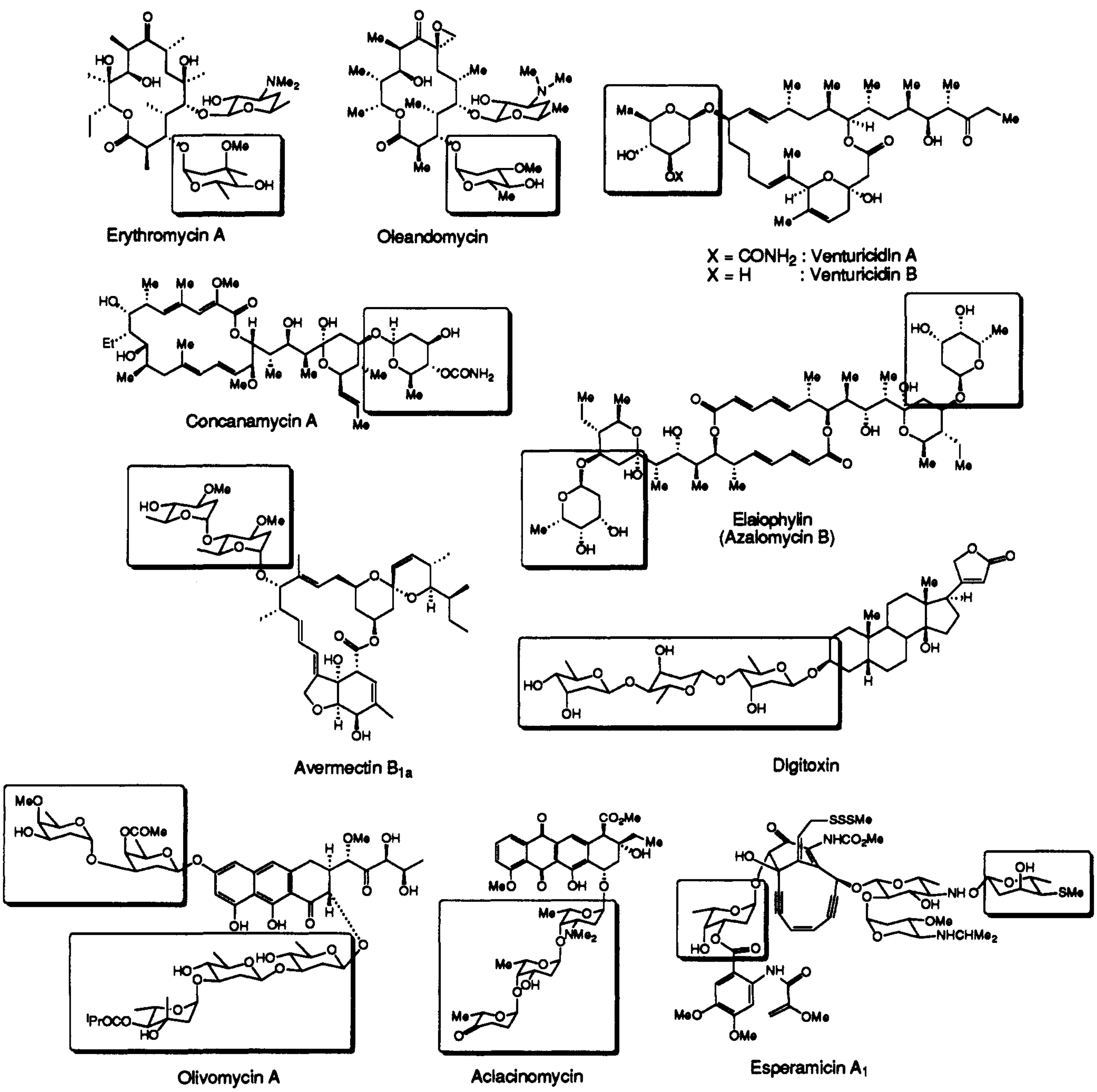
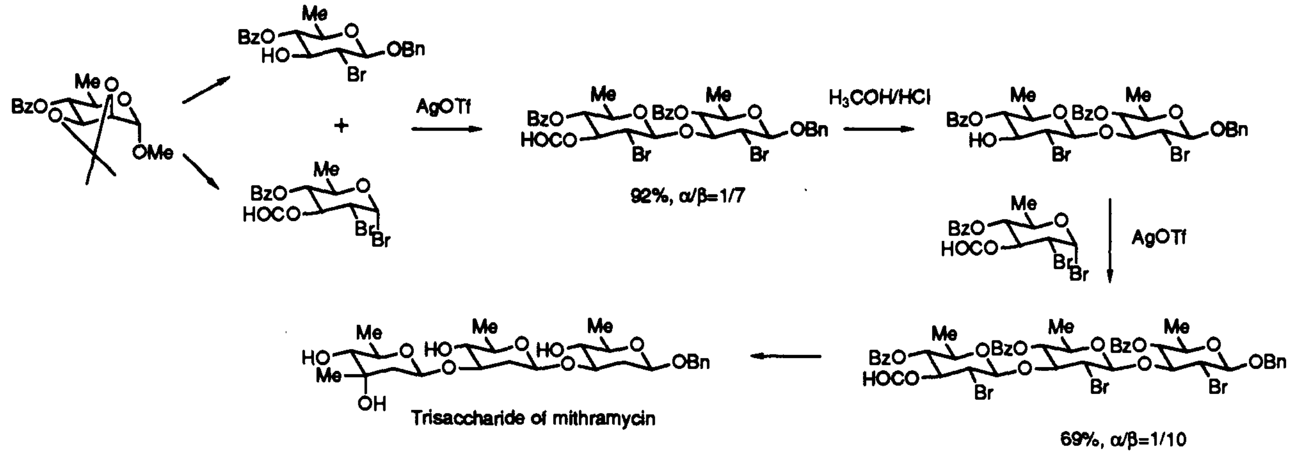
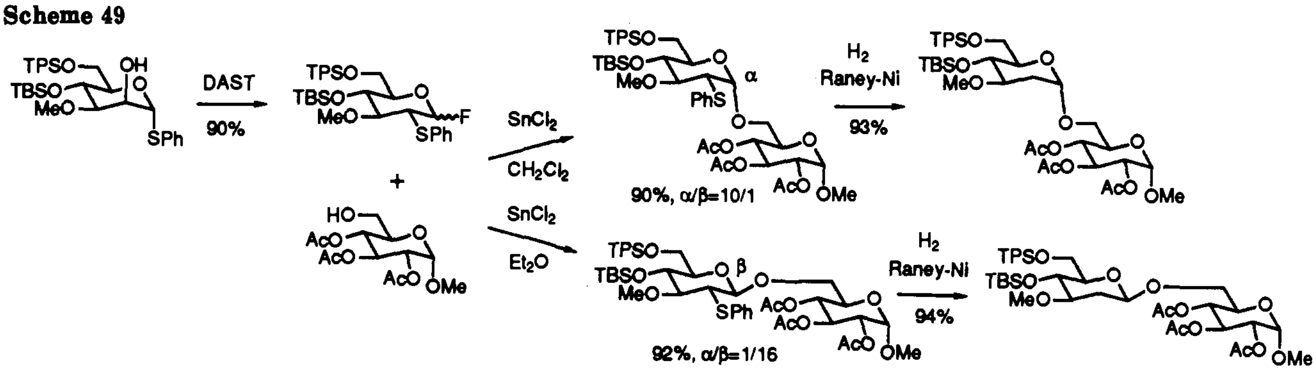


Figure 1. Some representative antibiotics having 2-deoxy (2,6-dideoxy) sugar.

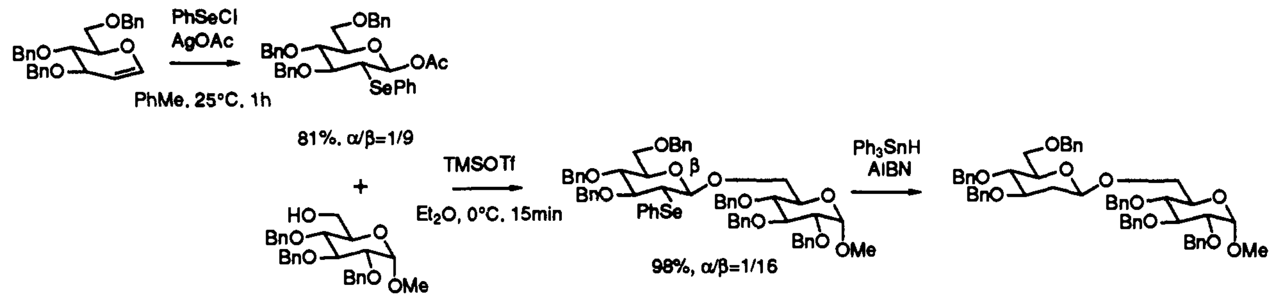
Scheme 48



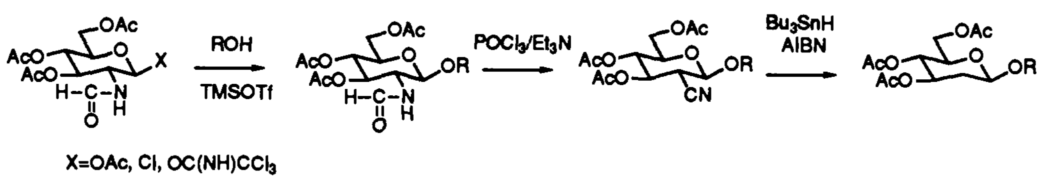
Scheme 49



Scheme 50



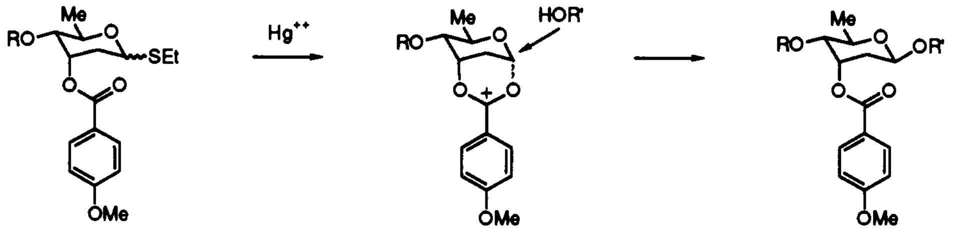
Scheme 51



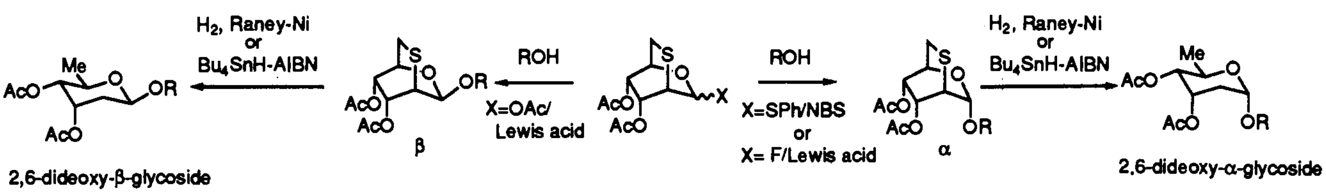
co-workers[164] introduced the use of 2-bromo-2-deoxyglycosyl bromides which have a bromide as a temporary participating group at the C-2 position for the β-selective glycosylation of complex aglycons. Silver triflate-promoted glycosidation of the 2-bromo-2-deoxy glycosyl bromides predominantly gave the corresponding β-glycosides which were effectively converted into the desired 2-deoxy-β-glycosides by reductive debromination. Combinational application of this methodology and NIS-method were effectively used in their convergent syntheses of the aureolic acid oligosaccharides[164d–f] (Scheme 48). Thiophenyl, selenophenyl, and N-formylamino groups were also employed as other temporary participating groups at the C-2 position which could be easily removed after glycoside formation.

In the method introduced by Nicolaou et al.,[165] 2-deoxy-2-phenylthioglycosyl fluoride was prepared from the corresponding phenyl thioglycoside *via* 1,2-migration with DAST and its glycosylation using $SnCl_2$ selectively gave both α- and β-glycosides by selecting a solvent in the reactions (Scheme 49). Beau and his co-workers[166] synthesized 1,2-*trans*-acetoxy selenides by treatment of glycals with PhSeCl and AgOAc and their glycosylations using TMSOTf predominantely afforded the β-glycosides (Scheme 50). On the other hand, several derivatives of N-formylglucosamine were employed as a glycosyl donor by Sinaÿ et al.[167] and the resulting β-glycosides obtained using TMSOTf were converted into the corresponding 2-deoxy-β-glycosides via the radical reduction of the intermediate isonitriles (Scheme

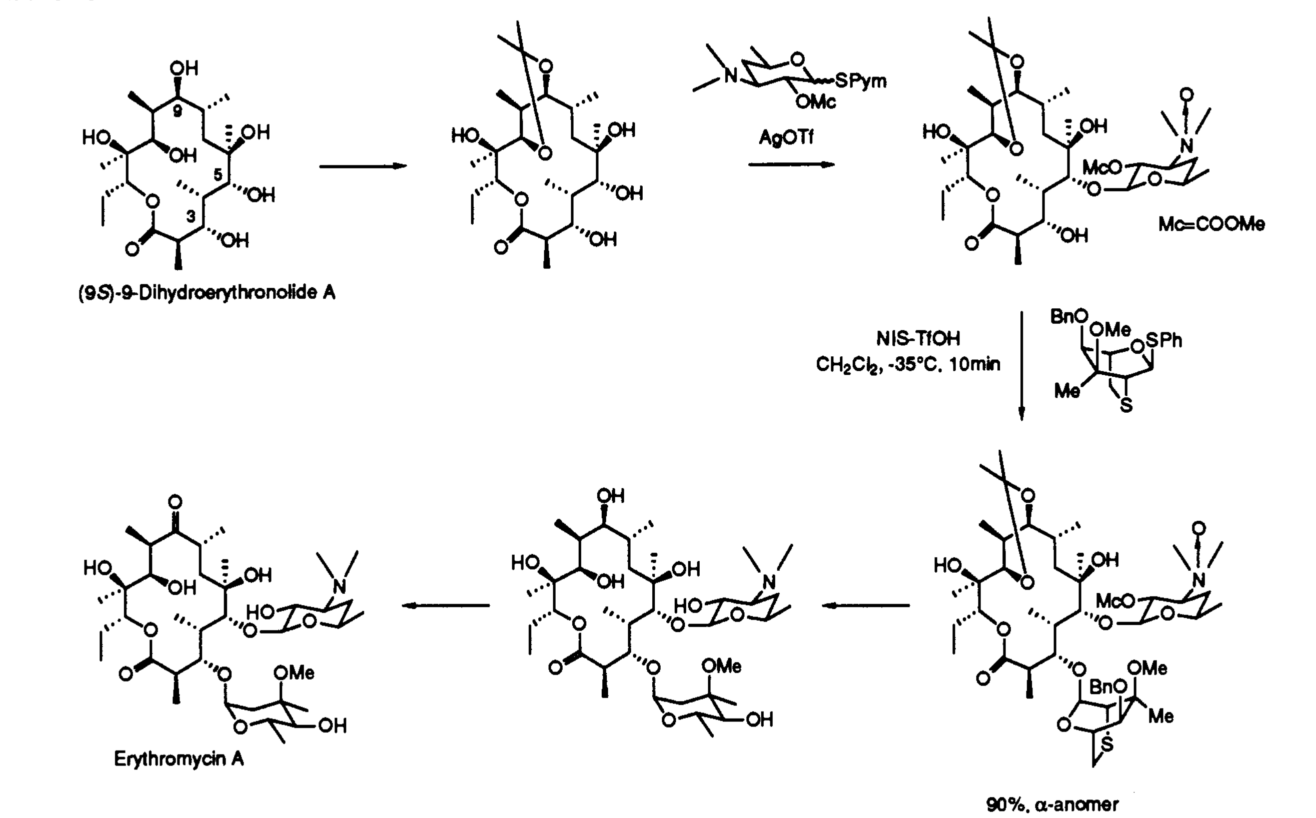
Scheme 52



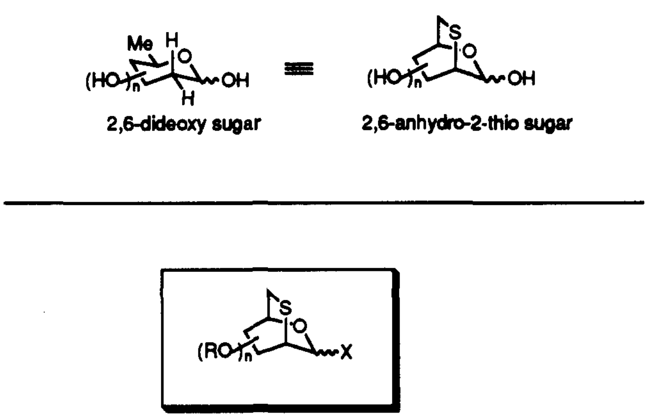
Scheme 53



Scheme 54



51). On the other hand, Wiesner and co-workers[30,168] reported an effect due to the participation by the *p*-methoxybenzoyl group attached to the C-3 position (Scheme 52). However, Binkley et al.[169] suggested that the participation from the C-3 position was not the dominating characteristic of glycosyl donors possessing an acyloxy group at the C-2 position. Recently, Toshima and Tatsuta[170] have designed conformationally rigid glycosyl donors, which have a thio bridge between the C-2 and C-6 positions, for the highly stereocontrolled syntheses of both 2,6-dideoxy-α- and β-glycosides (Figure 2). 2,6-Dideoxy sugar is a most common and important class of 2-deoxy sugars in bioactive natural products. Both glycosidations of 2,6-anhydro-2-thio sugars possessing a phenylthio group as an anomeric leaving group with NBS and glycosidations of 2,6-anhydro-2-thio fluorides with several Lewis acids in the presence of alcohols exclusively afforded the corresponding 2,6-anhydro-2-thio-α-glycosides in high yields. In contrast, 2,6-anhydro-2-thio-β-glycosides were predominantly obtained by the glycosidations of 2,6-anhydro-2-thio sugars having an acetoxy group at the C-1 position with alcohols in the presence of a Lewis acid. Further, the obtained 2,6-anhydro-2-thio-α- and β-glycosides were both effectively converted into the desired 2,6-dideoxy-α- and β-glycosides in high yields by hydrogenolysis using Raney Ni or radical desulfurization using n-Bu_3SnH and AIBN (Scheme 53). This novel method offered a new trend in highly stereoselective glycosylation, that is, effective utilization of the constructional features of the glycosyl residue in the stereoselective glycosylation reaction. Indeed, this method was effectively applied to their total synthesis of erythromycin A from its aglycon, erythronolide A and the 2,6-anhydro-2-thioglycosyl donor corresponding to L-cradinose[170c] (Scheme 54). On the other hand, the

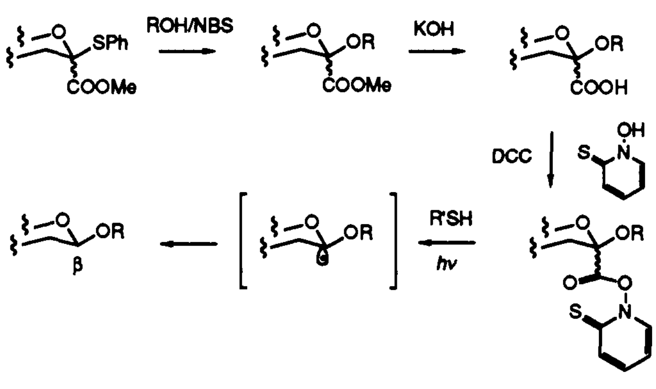


The 2,6-anhydro-2-thio glycosyl donor

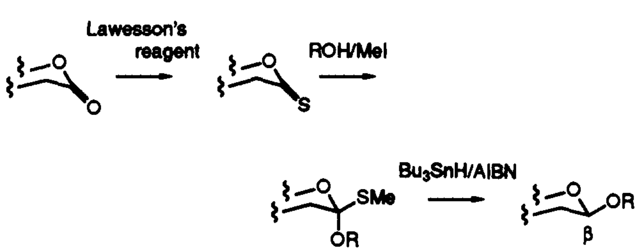
1. has a very rigid structure of the 2,6-anhydro-2-thio bridge.
2. could be a good precursor of 2,6-dideoxy glycoside.
3. The selectivity of glycosylation would not be affected by the anomeric effect.

Figure 2.

Scheme 55

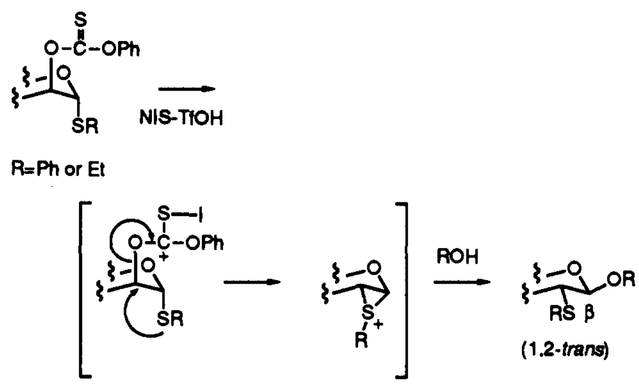


Scheme 56



interesting highly stereoselective syntheses of 2-deoxy-β-glycosides using alkoxy-substituted anomeric radicals were reported by two independent groups. Crich and his co-workers[171] developed the preparation of 3-deoxyulsonic acid glycosides from glycals and their reductive decarboxylation for the stereoselective syntheses of 2-deoxy-β-glycosides (Scheme 55). Kahne et al.[172] also synthesized the hemithio ortho ester from the lactone *via* the thionolactone and showed that the treatment of the hemithio ortho ester with n-Bu_3SnH and AIBN predominantly gave 2-deoxy-β-glycoside due to the high stability of α-directed anomeric radical (Scheme 56). Very recently, van Boom et al.[173] reported that the NIS–TfOH-mediated stereospecific glycosidation of ethyl (or phenyl) 2-*O*-(phenoxythiocarbonyl)-1-thioglycosides gave access to valuable 1,2-*trans*-linked oligosaccharides which afforded the respective 2-deoxy-α-manno- or

Scheme 57

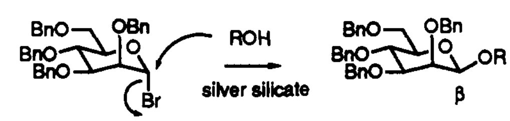


2-deoxy-β-glucopyranoside by desulfurization using Raney Ni (Scheme 57).

B. β-D-Mannoglycoside Synthesis

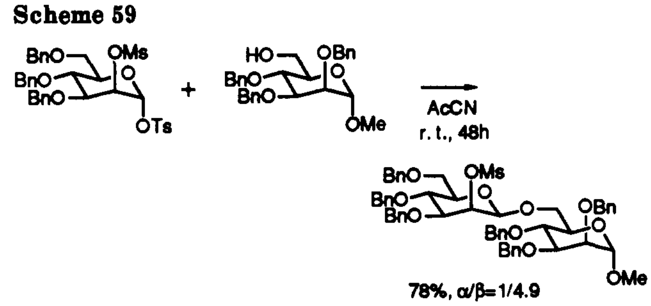
The β-manno-type linkage is a very important element in carbohydrate chains of glycoproteins. However, the stereoselective formation of a β-D-monnopyranoside bond is an especially difficult type of linkage to realize due to the steric repulsion of the 1,2-*cis* configuration and the instability due to the anomeric effect. In contrast, its isomer, α-D-mannopyranoside, is exclusively produced in the presence of a participating group at the C-2 position. Paulsen et al.[5] introduced a significant method for highly stereoselective β-D-mannopyranosides syntheses using benzyl-protected α-glycosyl bromides and insoluble silver catalysts such as silver oxide or silver silicate (Scheme 58). This

Scheme 58



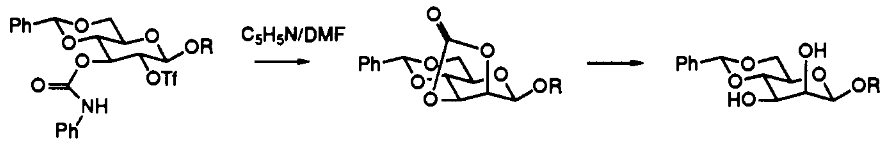
protocol is now well known as the heterogenic catalyst method. These reactions involved a replacement of the C-1 substituent with inversion. Schuerch et al.[116h,i] developed the use of sulfonyl groups at the C-1 and C-2 positions. Treatment of the 2-*O*-mesyl-1-*O*-tosylmannosyl donor with several alcohols in AcCN exclusively afforded the corresponding β-mannopyranosides with high stereoselectivities in high yields (Schemes 59). On

Scheme 59

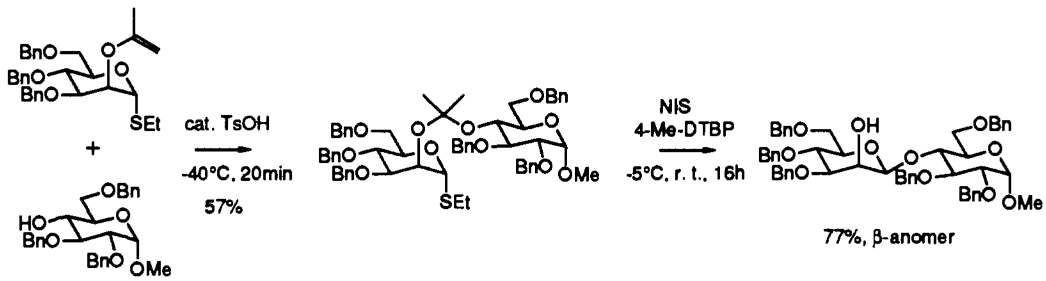


the other hand, Kunz and his co-workers[174] recently reported β-mannoside syntheses from β-glucoside *via* intramolecular substitution of the triflate group at the C-2 position by the phenylurethane moiety at the C-3

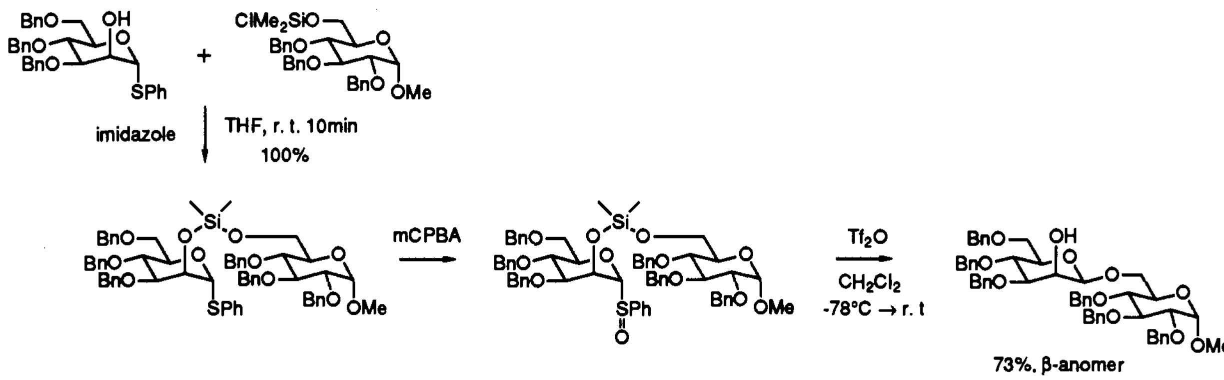
Scheme 60



Scheme 61



Scheme 62



position with inversion of the C-2 configuration (Scheme 60). Very recently, two other groups demonstrated unique approaches which focused on the configuration of the C-2 hydroxy group of β-mannopyranose. These methods commonly involved the formation of an intermolecular mixed acetal of the C-2 hydroxyl group and glycosyl acceptor and a glycosylation by intramolecular migration of the glycosyl acceptor to the anomeric position of the glycosyl donor. Indeed, Hindsgual et al.[175] used NIS as a promoter of the intramolecular reaction of ethyl thioglucoside (Scheme 61). Similarly, Stork et al.[176] employed a mixed Si-acetal and applied Kahne's method for activation of the phenyl sulfoxide of the glycosyl donor (Scheme 62). In these cases, the corresponding α-anomers were not produced at all.

XVII. Other Topics

A. Armed Sugar–Disarmed Sugar

Fraser-Reid and his co-workers[106a,107b,108] found a quite new and unique concept in the glycosylation reaction in 1988. In their extensive glycosylation studies of 4-pentenyl glycosides, the glycosyl donor possessing an acyloxy group with electron-withdrawing properties at the C-2 position was found to be much less reactive than the corresponding glycosyl donor having a benzyl group at the same position (eq 1 in Figure 3). The activated glycosyl donor and the deactivated glycosyl donor were called "armed sugar" and "disarmed sugar", respectively, by Fraser-Reid. Several pairs of armed–disarmed sugars are listed in Figure 3. This methodology made it possible to attach the armed sugar to the disarmed sugar, which had the same leaving group at the anomeric position, with high selectivity. In this glycosylation reaction, the self-coupling product of the disarmed sugar was not detected at all. Further, the obtained disarmed oligosaccharide could be converted into the armed oligosaccharide by transformation of an acyloxy group into a benzyl group at the C-2 position in two steps. The main reason for deactivation of the disarmed sugar is accounted to be the instability of the intermediate oxonium ion by a neighboring positive charge resulting from an electron-withdrawing group at the C-2 position (Figure 4). They also showed a armed and disarmed pair of reactants for synthesis of 2-deoxyoligosaccharides by using 2-bromo alcohol as a glycosyl acceptor[106a] (eq 2 in Figure 3). Although high stereoselectivity at an anomeric position was not realized in the 4-pentenylglycosylation methods, this concept opened a very convenient and useful way for the block synthesis of oligosaccharides. Van Boom and collaborators[46a] introduced a new glycosylation reaction with this concept using thioglycosides and IDCP as a promoter (eq 3 in Figure 3). In relation to these studies, Fraser-Reid et al.[107] and van Boom et al.[44] independently found that even these disarmed sugars could be activated by a more reactive activator such as NIS–TfOH. Further, Fraser-Reid et al.[177] reported a selective saccharide coupling by torsional effects in glycosides possessing an acetal protecting group (eq 4 in Figure 3). On the other hand, Danishefsky and his co-workers very recently applied this concept to the stereoselective

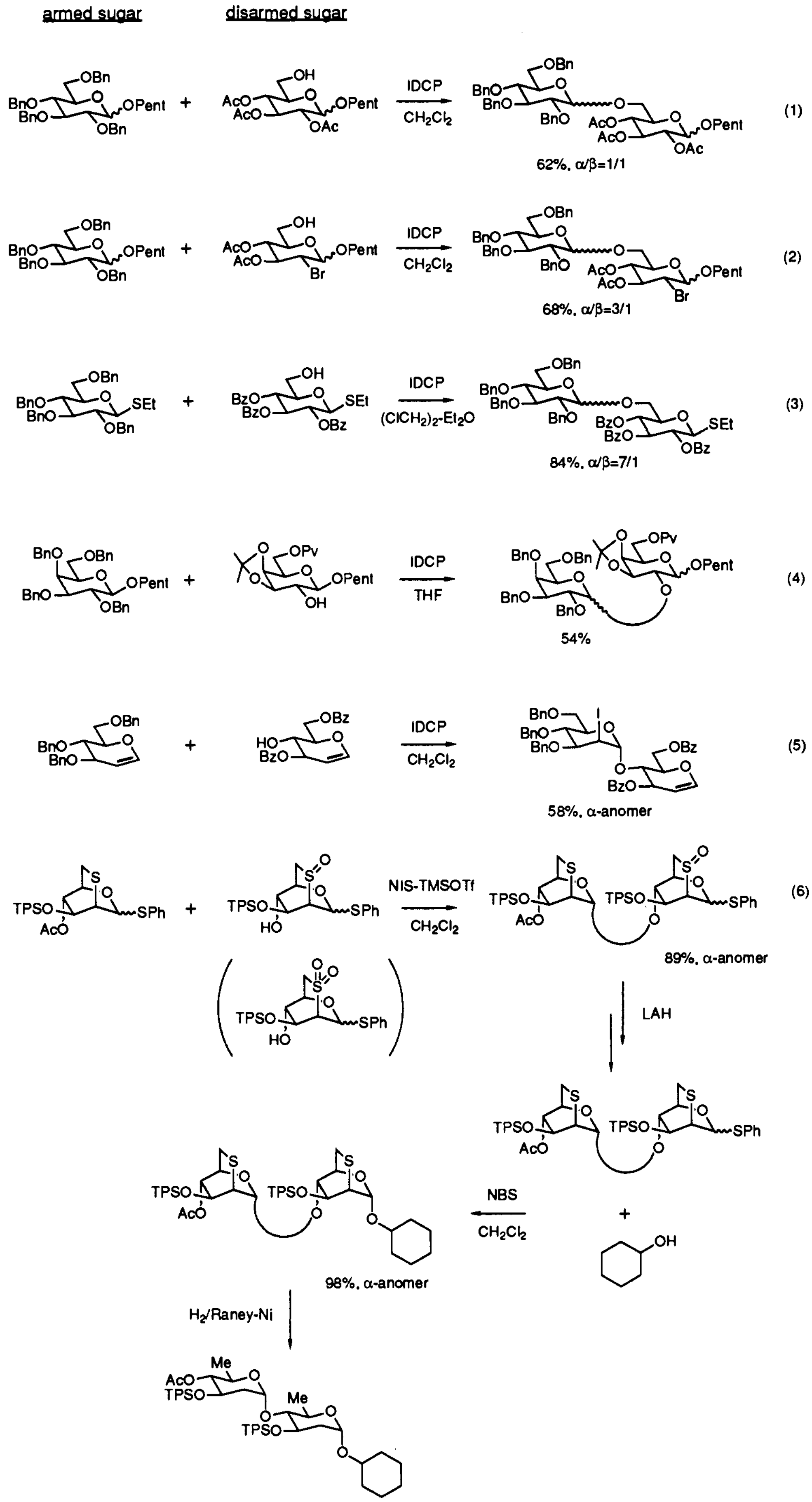


Figure 3.

glycosylation reaction of glycals in the presence of IDCP (eq 5 in Figure 3). In this case, differentiation of the C-3 protecting group of glycal was a significant factor for selective coupling. Toshima et al.[170e,f] also intro-

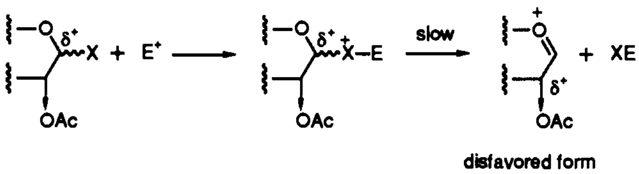


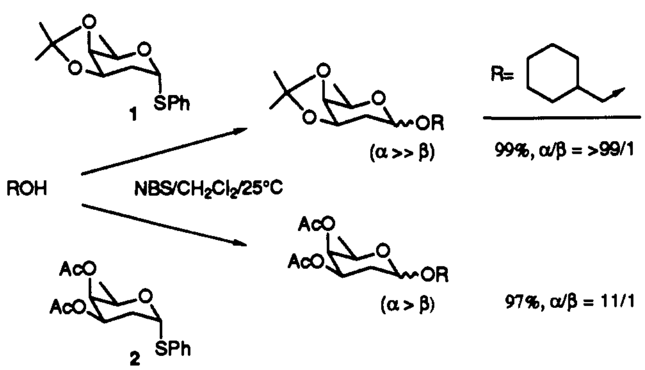
Figure 4.

duced new armed and disarmed sugars in their highly stereocontrolled glycosylation method using 2,6-anhydro-2-thio sugars (eq 6 in Figure 3). The reactivities of 2,6-anhydro-2-sulfinyl- and 2,6-anhydro-2-sulfonyl-glycosyl donors were both found to be much lower than that of the corresponding 2,6-anhydro-2-thio glycosyl donor. Therefore, the 2,6-anhydro-2-thioglycosyl donor was selectively coupled with the corresponding 2,6-anhydro-2-sulfinyl glycosyl acceptor to afford the disarmed oligosaccharide with high stereocontrol in high yield. Further, the obtained disarmed oligosaccharide could be easily converted into the armed oligosaccharide by simple reduction of the sulfoxide moiety using LAH. This method was effectively applied to stereoselective synthesis of avermectin's 2,6-dideoxy-α-disaccharide moiety.[170f]

B. Conformational Assistance of Glycosyl Donor

Recently, Toshima and Tatsuta[178] demonstrated a highly stereoselective glycosylation by conformational assistance of the glycosyl donor. In a number of glycosylation studies, many factors such as the type of leaving group at the anomeric position, their promoter, the temperature, the solvent and the substituents of the sugar were widely examined in order to get high stereoselectivity. On the other hand, little attention has been paid to the conformation of the glycosyl donor in anomeric stereoselectivity. Toshima and Tatsuta designed the conformationally rigid glycosyl donor 1 possessing a 3,4-*O*-isopropylidene group and showed that the selectivities of the glycosidations of 1 with several alcohols by NBS were much higher than those of the glycosyl donor 2 having the same configuration (Scheme 63). Therefore, it seems reasonable to understand that the high stereoselectivity of the glycosylation reaction of 1 resulted from both the strong repulsion of the 1,3-diaxial interaction between the C-3 substituent and the approaching alcohol which was generated from its conformational assistance and the anomeric effect[179] (Figure 5). The MM2 calculation of the conformations of the reactive oxonium intermediates using new MM2 parameters for the oxonium ions recently published by Houk[180] also assisted in this explanation.[181] The boat type of oxonium intermediate 3 deriving from the glycosyl donor 2 does not locate as a stable form in optimization and is transformed into the stable conformation 4 during minimization of the energy. In contrast, MM2 calculations and the Boltzmann distribution of the comformers indicated that the thermodynamic equilibrium of the conformations 5 and 6 deriving from 1 at 25 °C would exist in a ratio of 53:47 (Figure 6). These results strongly suggested that the conformational assistance of the glycosyl donor as well as other factors mentioned above was an indispensable factor in glycosylation stereoselectivity and could be used for controlling the stereoselectivity.

Scheme 63



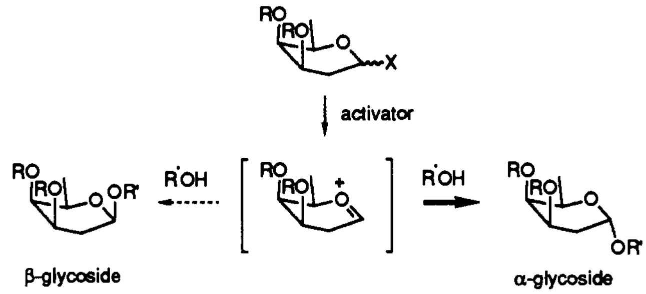


Figure 5.

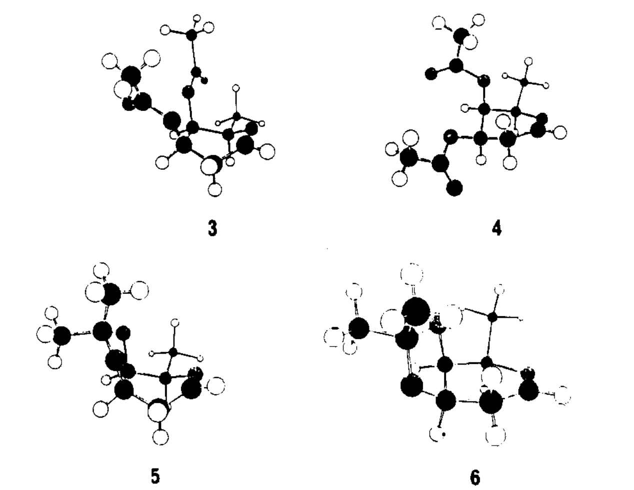
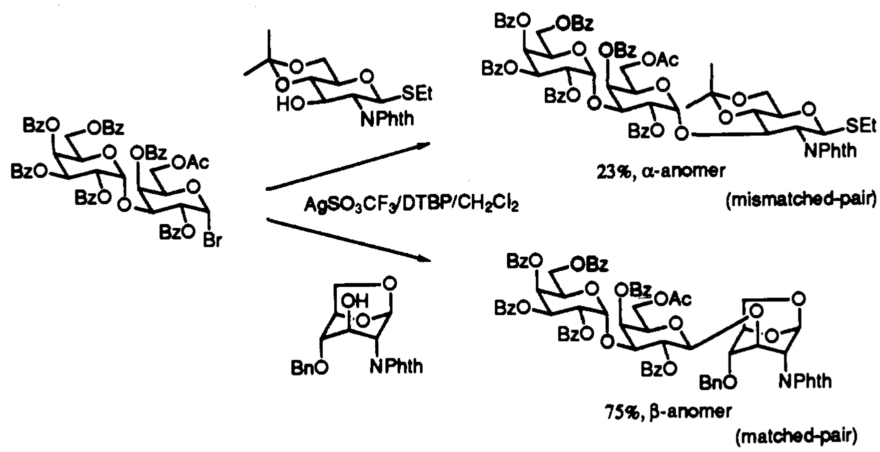


Figure 6.

C. Double Stereodifferentiation (Matched–Mismatched Glycosylation)

Van Boeckel et al.[182] very recently indicated very interesting and unexpected glycosylation results. In general, it is believed that the glycosyl donor possessing an acyloxyl group with a participating function at the C-2 position exclusively gave the corresponding 1,2-*trans* glycoside with quite high stereoselectivity in any glycosylation reaction. However, they clearly showed that even the stereoselectivity of glycosidation of the C-2 benzoyl-protected glycosyl donor was dramatically changed by the structure of the glycosyl acceptor (Scheme 64). They also suggested that steric interaction between a glycosyl donor and an acceptor in the transition state strongly influenced the stereochemical results of glycosylations and when a desired configuration of the anomeric position is needed the protecting

Scheme 64



groups or the conformation of the glycosyl donor and/ or acceptor may have to be changed.

XVIII. Concluding Remarks

In spite of considerable progress in the O-glycosylation method, a powerful method and general aspects for glycosylation has not yet appeared from the point of view of chemical yield and stereoselectivity. Therefore, we always ask the question as to which method is the most suitable in our synthesis. Further, general chemical methodologies for the O-glycosylation of a totally unprotected free sugar and the O-glycosylation in water such as enzymatic glycosylation[183] have still not been realized. Does a single powerful method in the glycosylation area really exist? In the future, two alternative ways may determined an efficient glycosylation reaction. One way is development of a more general method. Another way is creation of the special method which is peculiar to each type of sugar considering the feature of each sugar structure. A representative example of the latter is the 2,6-anhydro-2-thio sugar method for 2,6-dideoxy glycosides synthesis. Since sugar is an indispensable biosubstance in our life activity, the study of O-glycosylation will be continued for a long time.

Notes Added in Proof

After submission of the original manuscript, several reports have appeared in the literature. These works are briefly mentioned below under the appropriate sections where they should be inserted.

Section II.A. Nishizawa et al. reported a zinc salts catalyzed α-rhamnosylation using glycosyl chloride as glycosyl donor.[184]

Section III. Kusumoto and his co-workers reported the use of iodosobenzene–triflic anhydride as an efficient promoter for glycosylation reaction of thioglycosides.[185]

Section IV. A novel stereoselective glycosidation of pentaacylglucopyranose and alkyl silyl ether using methyltrichlorosilane and silver perclorate was demonstrated by Mukaiyama et al.[186] Also, Mukaiyama et al. reported a new glycosylation promoted by a catalytic amount of $Sn(OTf)_2$ for synthesis of 2-amino-2-deoxy-β-D-gluco- and -galactopyranosides.[187]

Section VII. Nicolaou et al. effectively applied trichloroimidate method to his elegant first total synthesis of enediyne antibiotics, caliheamicin γ_1^I.[183]

Section XIV. Toshima et al. reported that glycosidation of glycal with alcohol by DDQ as a catalytic promoter proceeded to give the corresponding 2,3-unsaturated glycosides in high yields.[189]

Section XV. A new glycosidation of 3,4-dimethoxybenzyl 2-deoxyglucopyranosides by DDQ was reported by Inanaga et al.[190] Higashi et al. developed a glycosylation method by combined use of trimethylsilyl halide and zinc triflate to promote several glycosyl esters and alkyl glycosides as glycosyl donors.[191]

Section XVI.A. Toshima et al. accomplished a highly stereoselective total synthesis of 2,6-dideoxytrisaccharide of olivomycin A by the application of glycosylation reactions using 2,6-anhydro-2-thio sugars.[192]

Section XVI.B. A similar method to Stork's protocol which involved intramolecular glycosidation with a silylene-connected aglycon described in this section was independently announced by Bols for stereoselective synthesis of α-glucosides.[193]

Abbreviations

Ac	acetyl
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
Bn	benzyl
Bz	benzoyl
Bu	butyl
t-Bu	*tert*-butyl
Cp	cyclopentadienyl
CSA	*dl*-10-camphorsulfonic acid
DAST	(diethylamido)sulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEIPS	diethylisopropylsilyl
DIBAL	diisobutylaluminum hydride
DMF	dimethylformamide
DTBP	2,6-di-*tert*-butylpyridine
DMTST	dimethyl(methylthio)sulfonium trifluoromethanesulfonate
Et	ethyl
HMPA	hexamethylphosphoric triamide
IDCP	iodonium dicollidine perchlorate
IPDMS	isopropyldimethylsilyl
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LPTS	2,6-lutidinium *p*-toluenesulfonate
mCPBA	*m*-chloroperoxybenzoic acid

Me	methyl
Ms	methanesulfonyl
MPM	*p*-methoxybenzyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
Pent	4-pentenyl
Ph	phenyl
Phth	phthal
Pr	propyl
i-Pr	isopropyl
PPTS	pyridinium *p*-toluenesulfonate
Pv	pivaloyl
r. t.	room temperature
SE	2-(trimethylsilyl)ethyl
SEM	[2-(trimethylsilyl)ethoxy]methyl
TBPA	tris(4-bromophenyl)ammoniumyl hexachloroantimonate
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	(trifluoromethyl)sulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TMU	1,1,3,3-tetramethylurea
Tr	triphenylmethyl
TPS	*tert*-butyldiphenylsilyl
Ts	*p*-toluenesulfonyl

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