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The Synthesis of 2-Deoxyglycosides: 1988–1999

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Dedicated to Professor Dr Joachim Thiem on the occasion of his 60th birthday

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1. Introduction

The synthesis of 2-deoxyglycosides is a small, but important niche in the field of carbohydrate chemistry. Although in any one year many more 2-oxy and 2-aminoglycosyl linkages are forged in synthetic chemistry laboratories,[1] the preparation of the 2-deoxyglycosyl function, found in several important antibiotic families, is an interesting and non-trivial goal. When one considers the general case of the crucial bond-forming sequence in glycosyl transfer (Scheme 1), a carbohydrate intermediate **2** with an electrophilic and essentially trigonal C-1 is usually visualized. The electrophilicity is normally induced by the departure of a leaving group at C-1 or by electrophilic attack on a C1–C2 (glycal) double bond. Whether the orientation of the glycoside bond is α or β depends on some combination of control elements. One presumed control element is commonly known as the 'kinetic anomeric effect'. There is a well-known thermodynamic effect ('the anomeric effect') in tetrahydropyrans which favors axial linkage of electronegative functional groups to C-1. It is thus assumed that this thermodynamic 'anomeric' effect exerts its influence in the transition-state for bond-forming to the electrophilic C-1, hence axial (or α) bond formation. In fact, the axial preference for the incoming nucleophile may be better viewed as the general stereoelectronic effect that favors axial attack in any 6-membered ring. Thus, when electrophilic carbon at C-1 is approached from the 'axial' face the transition-state must develop as a chair form **4**. When the same electrophilic carbon is approached from the 'equatorial' face, the transition-state must develop as a boat-like species **6** which is approximately 5 kcal/mole higher in energy than the chair form. Only after an axial-like bond is formed can the boat relax to a chair with an equatorial substituent **8**. These stereoelectronic arguments are only relevant in product-like 'late' transition-states. A second control element at C-1 is the neighboring group participation of a C-2 substituent that can act as a Lewis base toward the electron-deficient C-1 (Scheme 2). If the group at C-2 is equatorial as in **9** (glucose configuration), then it interacts with C-1 so as to block the α face (**10**), thus favoring β-face attack of the external nucleophile. Alternately, an axial group at C-2 (**12**, mannose configuration) would interact with C-1 so as to block the β face (**13**), thus favoring α-glycoside formation. It should be noted that some versions of **10** and **13** in Scheme 2 can be formed directly by attack of electrophiles on glycals. There are few examples of participation by groups at

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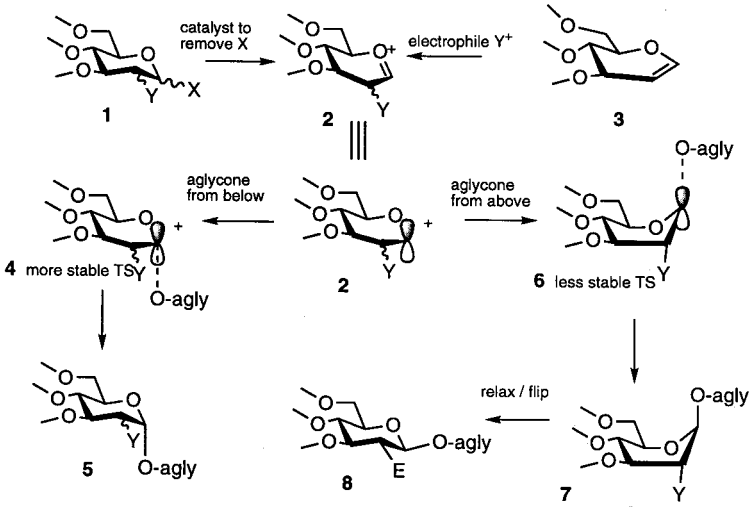
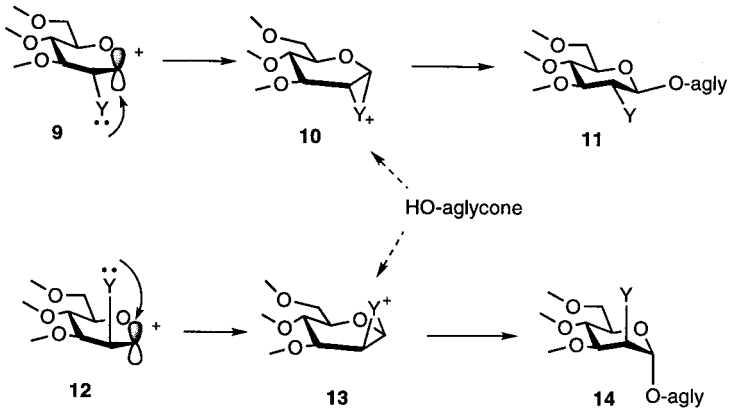
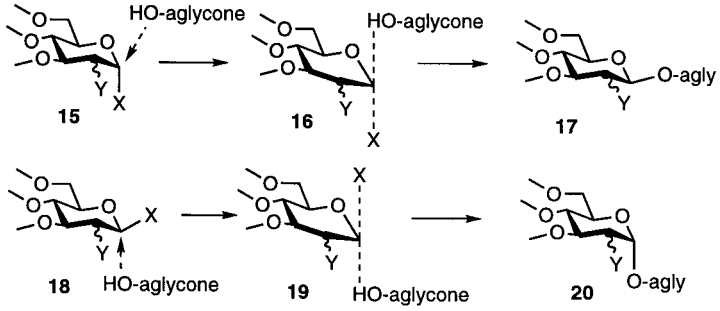


Scheme 1.



Scheme 2.



Scheme 3.

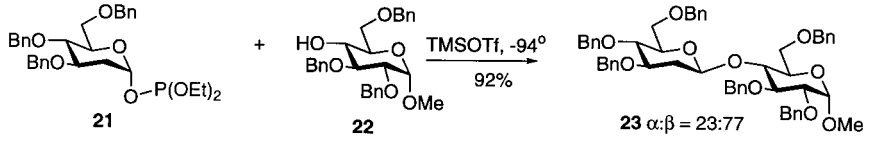
other locations on the carbohydrate periphery. The least common element of control is based on the assumption that the electrophilicity of C-1 can be controlled by reaction conditions so that the carbon remains tetrahedral and is substituted in an S_N2-like way to give strict inversion of configuration (Scheme 3). In this review of work which has been published since the last landmark survey by Thiem and Klaffke,[2] the reader will encounter all these possibilities for control of the stereochemistry of glycosyl transfer in the synthesis of 2-deoxyglycosides. When control elements at C-2 are involved in the glycosylation step, there will be additional chemistry required to remove the control element to finally obtain a 2-deoxyglycoside. In order to keep the review to a manageable size, the examples chosen will be for the synthesis of hexopyranosyl *O*-glycosides linked to natural aglycones or realistic models. Examples of methyl, ethyl etc., will normally not be discussed. Also omitted is the chemistry of

sialic acid glycosyl transfer and glycosidations via the Ferrier reaction. Literature coverage dates from the last major review of Thiem and Klaffke up to late 1999. Interested readers are also referred to a 1997 review by Kirschning, Bechtold and Rohr,[3] which focuses on the more biochemical aspects of 2-deoxy sugars and their oligosaccharides and to a 1999 review by Hallis and Liu[4] on the mechanistic aspects of deoxy sugar formation.

2. Methods and Examples

2.1. No control element at C-2

Phosphites have been used as 2-deoxyglycosyl donors by two labs under quite different conditions with correspondingly different outcomes. Hashimoto[5] formed diethyl phosphites of five different pyranose donors at −78° and obtained principally α-phosphites with the exception of dibenzyl-L-fucose where the α anomer was favored by a factor of only 2. Then, with catalysis by 0.1 equiv. of TMSOTf at −94°, rapid glycosyl transfer took place to afford good yields of glycoside favoring the β-product (Eq. (1)) with a range of acceptors with the poorest selectivity in the glucose series being 29:71 and the best 90:10 with the glaring exception of phenol as the acceptor where the α anomer was favored (α:β=71:29). Other deviations from β selectivity occurred with a galactose donor and a hindered glucose acceptor (α:β=69:31) and a fucose donor with an unhindered glucose acceptor (67:33 α:β) and with cyclohexyl carbinol (α:β=45:55). Paterson, using essentially the same 2,6-dideoxyglucosyl diethyl phosphite donor, differing in protecting groups (Paterson-3-DEIPS, 4-carbamate; Hashimoto-3,4-dibenzyl) with BF_3–Et_2O at −78° or $ZnCl_2$ at 0°, obtained modest (and unwanted) α-selectivity in the preparation of a concanamycin synthon (Eq. (2)).[6] Hashimoto had observed outstanding β-selectivity with his conditions. Also in contrast to Hashimoto, Schmidt[7] reports the phosphitylation of 2-deoxy triacetylglucose and galactose with trichloroethyl phosphorochloridite to produce 2:1 and 5:2 α:β mixtures of phosphites. These were then activated with a catalytic amount of BF_3–Et_2O at room temperature, $Sn(OTf)_2$ or TMSOTf (−40°) and coupled with 3 different glycosyl acceptors affording principally α-configured disaccharides (Eq. (3)). It is interesting to note that with a fructofuranose donor, α:β selectivity is inverted when TMSOTf was used in place of $Sn(OTf)_2$. In a variation on this theme, Zhao examined the phosphoramidites of tribenzyl-2-deoxyglucose and galactose. These phosphoramidites, upon activation with 1.5 equiv. of TMSOTf at −78° coupled cleanly with three different glycoside acceptors to afford α-disaccharides in high yield and anomeric selectivity (from 99:1 to 91:9, Eq. (4)).[8] The 2-deoxytriacetyl glucosyl diphenyl phosphate donor, generated by a novel rearrangement is a reactive species producing α-disaccharides in good yield with moderate selectivity, ranging from 2.3–4.5 to 1. The catalyst for use with primary acceptors is simply 0.1 equiv. of anhydrous $MgClO_4$ whereupon reactions were complete within 15 min. With no catalyst the reaction required 24 h. A Lewis acid catalyst was obligatory for secondary acceptors (Eq. (5)).[9]



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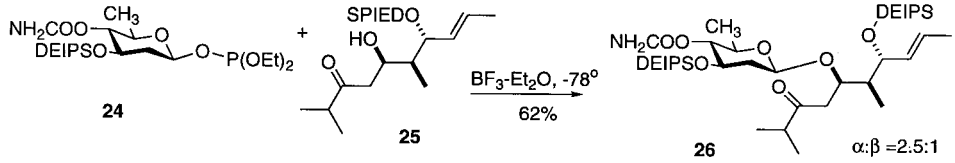

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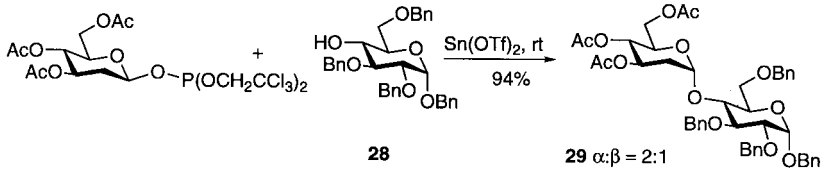

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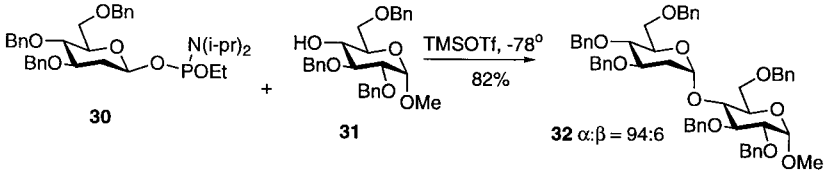

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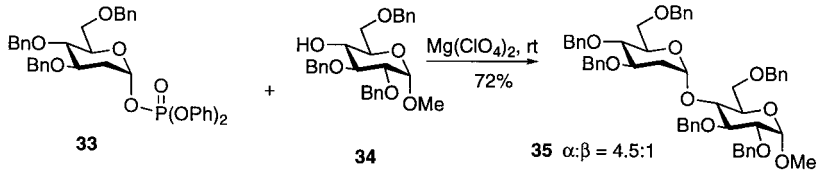
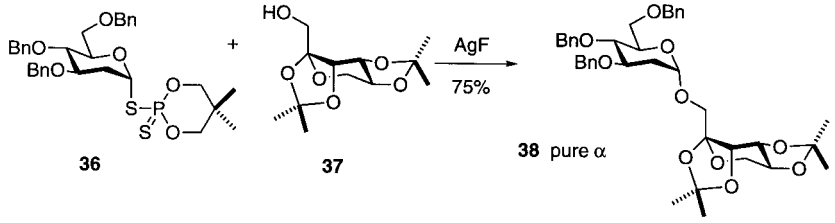


(5)

Phosphorodithioates are novel sulfur-based leaving groups for use in glycosyl transfer. Bielawska and Michalska report 2-deoxytriacetyl glucose and galactose donors as well as a 2-deoxytribenzyl glucose donor reacting with three common acceptors, namely 1,2,3,4-diisopropylidene galactose, 1,2,5,6-diisopropylidene glucose, and 2,3,4,5-diisopropylidene fructopyranose (Eq. (6)). The couplings were run in either dichloromethane or acetonitrile in the presence of 2.7 equivs. of AgF as promoter. The benzyl donor gave the highest α-preference with perfect selectivity in the case of the fructopyranose acceptor. The galactose donor gave α:β=92:8 selectivity with the same acceptor.[10] Using either NIS or I(sym-collidine)$_2$ perchlorate as promoter, Thiem demonstrated the broad utility of the phosphorodithioate family of 2-deoxyglycoside donors (8 different donors) with improved α-selectivity compared to the AgF promotion (Eq. (7)). For example, in the coupling of the 2-deoxygalactosyl donor with the diisopropylidene acceptor, the α:β selectivity was 55:45 and 91:9 for AgF and NIS promotion, respectively.[11] A related phosphorus derivative, the phosphinothioate of 2-deoxy-tribenzyl glucose activated by trityl perchlorate in benzene solvent was shown to glycosylate cholestanol, diisopropylidene galactose and a 1,6-anhydrogalactose derivative. A 30% mole ratio of trityl perchlorate was used and the α selectivity ranged from 20:1 to 5:1. Although it was suggested that the transfer occurred via an S_N2 mechanism, there was no convincing evidence presented (Eq. (8)).[12]



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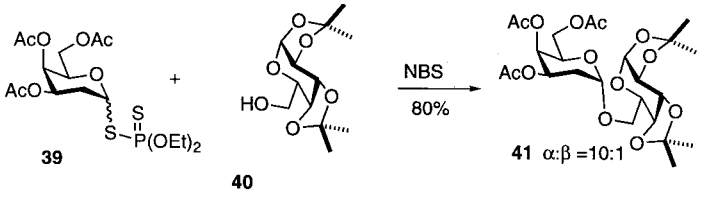

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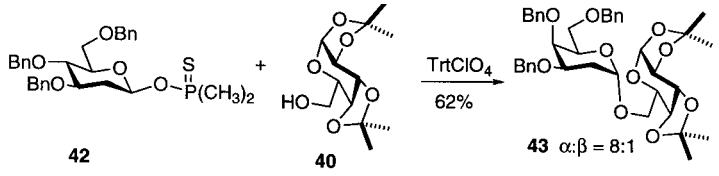
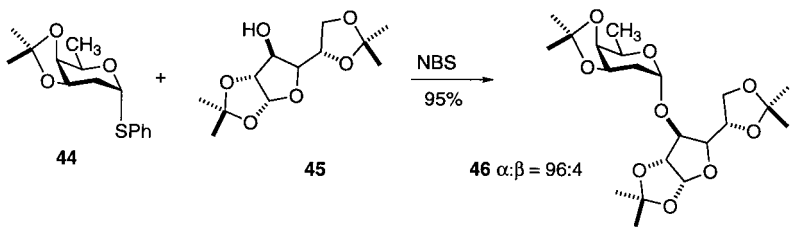


(8)

A novel thioether activation method has been described by Zhao. To date, the use of bis(trifluoroacetoxy)iodo benzene has been described only for the preparation of ethyl glycosides; but the glycosyl transfer apparently takes place with clean inversion at the anomeric center.[13] A more conventional activation of thioglycoside donors has been described by Tatsuta in a study of four different 2,6-dideoxyhexose donors and six different solvents with cyclohexylmethanol as the acceptor. The isopropylidene derivative gave the highest α-selectivity, attributed by the authors to a boat-like conformation where the 3-substituent is axial-like and blocks the β-face. In the opposite stereochemical series, essentially no selectivity is observed. The most selective α-donor also glycosylated diisopropylidene glucose in both excellent yield and stereoselectivity (Eq. (9)).[14] The Kahne group has developed a powerful glycosidation method known as the sulfoxide activation route. It has been applied to the synthesis of the vancomycin disaccharide. Two equivalents of phenylsulfoxide donor were activated at −78° with 1 equiv. of triflic anhydride which led to glycosylation of the 2-OH of a model phenyl glucoside to form exclusively α-glycoside in 71% yield (Eq. (10)).[15] Ley has developed the phenylsulfonyl group for glycosyl transfer, and has applied it to 2 examples in the 2,6-dideoxyglucose series. The examples shown use 5 equiv. of acceptor and $MgBr_2{\cdot}Et_2O$ catalyst to afford good yields of principally α-glycoside (Eq. (11)).[16]



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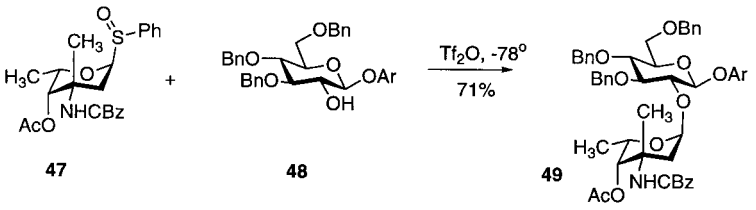

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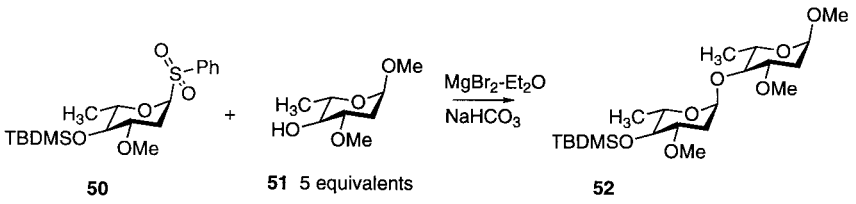
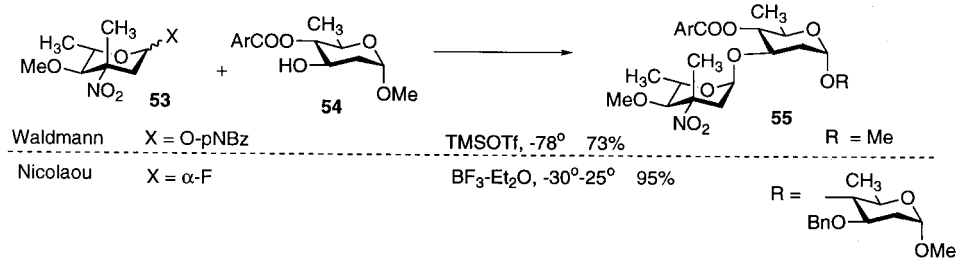


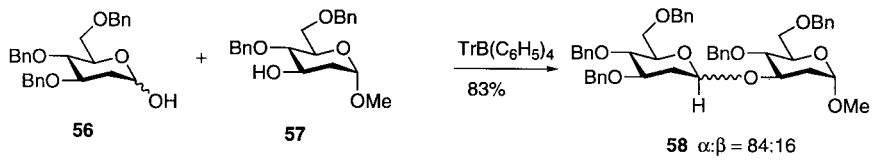
(11)

3-Nitro sugars display interesting properties as both donors and acceptors in 2-deoxyglycosyl transfer. In work on the everninomicin antibiotics, Scharf reported that the *p*-nitrobenzoate of evernitrose, upon activation at −78 with TMSOTf, afforded α-glycoside cleanly in 73% yield with the substituted olivose acceptor. Note the serious 1,3-diaxial repulsion between the 3-methyl group and the glycoside linkage (Eq. (12)).[17] Nicolaou reports a similar outcome with the fluoride donor of evernitrose where $BF_3{\cdot}Et_2O$ catalysis affords a 95% yield of α-glycoside.[18] Also noteworthy is the subsequent chemoselective Pd/H_2 debenzylation which leaves the nitro group untouched. A striking effect of the neighboring 3-substituent of the 4-hydroxyacceptor on selectivity has been reported by Giuliano in his work with decilonitrose.[19] Thus, when the acceptor 3-axial substituent was *N*-acetyl, a modified Koenigs–Knorr coupling with diacetoxyfucosyl bromide yielded an α:β=2:3 mixture. When the 3-axial group was *N*-trifluoroacetyl or nitro, the α selectivity was 30:1 and 100:0, respectively. There is no obvious explanation for this effect in the product-forming step. It may be that the α isomer in the *N*-acetyl series is not kinetically stable under the reaction conditions and thus epimerizes, whereas the more electron-withdrawing groups in the other series retard protonation of the glycosidic oxygen sufficiently to prevent epimerization.



(12)

Mukaiyama[20] has described the optimization of a simple glycosidation using unactivated tribenzyl-2-deoxyglucose as the donor catalyzed by 5 mol % of trityl tetrafluoroborate in a solvent mixture of benzene/toluene 10:1 in the presence of 1 g of Drierite/mmol of substrate (Eq. (13)).[21] The acceptor list includes two examples of 6-hydroxyglucose materials, two cases of 3-hydroxyglucose derivatives, cholestanol, cyclohexanol and *n*-octanol. Yields ranged from 82 to 93 % and α:β ratios were found from a low of 83:17 to a high of 91:9. Similarly, Toshima reports that tribenzyl-2-deoxyglucose can be induced to glycosylate a 6-hydroxyglucose derivative (used in 3-fold excess) in 74% yield with α:β=86:14 using the novel heteropoly acid $H_4SiW_{12}O_{40}$. The catalyst is also successful in a glycosyl transfer to the 4-OH of 1,6-anhydro-3-benzyl-2-azidoglucose (82%, α:β=90:10).[22] The catalyst system is also effective with simpler acceptors. Glaudemans reports that the TBDMS glycoside of 3,4,6-tribenzoylglucose can be a donor to the 6-OH of methyl-2,3,4-tri-*O*-benzyl-α-glucoside (selectivity indicated as α).[23] In a follow-up of older work from the New Brunswick group, Finizia examined the synthesis of aminoglycosides of cardiac-active steroids using glycosyl donors where an axial 3-carbamate was positioned for 1,3-(axial) participation with the anomeric carbon so that 2-deoxy-β-glycosides might be selectively formed (Eq. (14)). Unlike the earlier work, there was very little selectivity observed, using thioglycoside leaving groups or trichloroacetimidate leaving groups. The best case with a modest β:α ratio of 1.7:1 was observed with a classical Fischer–Helferich glycosylation using as donor the free anomeric OH in benzene with *p*-TosH as catalyst, suggesting to the present authors that this is simply the thermodynamic result.[24] A modified Fischer–Helferich procedure has been used to prepare a derivative of ethylene glycol for use in linking to a tryptamine. The stereochemical outcome is not described.[25]



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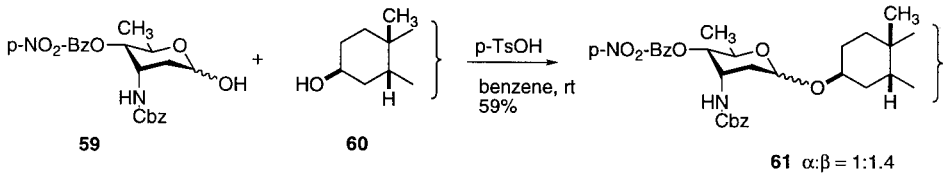
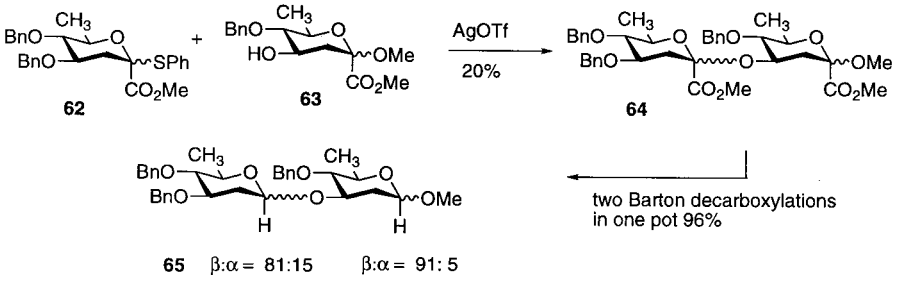


(14)

A unique approach to β-glycosides was developed simultaneously by Crich and Kahne, namely introduction of the anomeric axial hydrogen via radical chemistry as the ultimate step in a synthesis where the glycosidic bond between the anomeric oxygen and the aglycone had been pre-formed. Crich's approach[26] begins with the preparation, in a non-stereocontrolled manner, of glycosides of ulosonic acids. Then Barton decarboxylation of these glycosides forms an anomeric radical which is preferentially trapped by hydrogen atom donors from the α face. This approach is successful in both the 2-deoxygluco- and galactose series and with aglycones including chloesterol, phenols and carbohydrates. The minimum β:α ratio reported was 8:1 and often exceeded 10:1 (Eq. (15)). Perhaps the one drawback to the method is the less-than-ready availability of the ulosonic acid precursor. The Kahne approach[27] to the same anomeric radical as described above required the synthesis of the monothio *ortho* ester glycoside from a precursor thiono lactone (Eq. (16)). Then, standard tributyl tin hydride chemistry produced the desired β-glycosides with the same sorts of selectivities observed by Crich. In the 2-deoxy series, only the methyl glycoside was prepared. The limitation in the Kahne approach is the tricky preparation of the monothio *ortho* ester and its thionolactone precursor.



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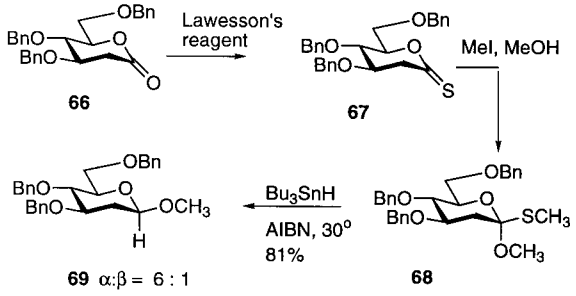
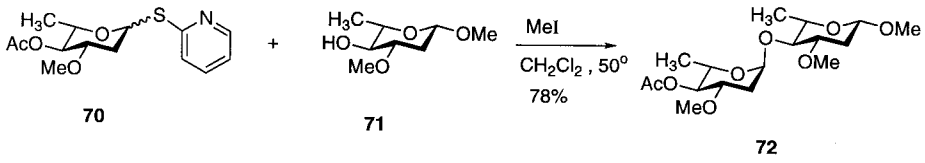


(16)

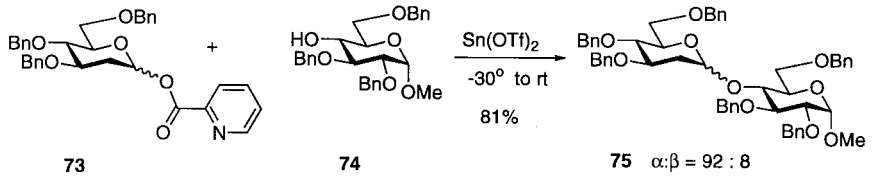
The unusual 2-pyridylthioglycoside leaving group, when activated with methyl iodide, affords α-linked disaccharides in yields of 65–87% with 2-deoxyglucose, 2-deoxygalactose and 2,6-dideoxyglucose donors.[28] Both 6- and 4-equatorial hydroxyls acted as acceptors and formed products with essentially perfect α-selectivity except with 1,2,3,4-diisopropylidene galactose where the selectivity degrades to 85:15 α:β. The method was used to prepare the crystalline avermectin disaccharide in 78% yield as a single anomer by Mereyala using the pyridylthioglycosyl oleandrose as donor and methyl iodide as catalyst (Eq. (17)).[29] The method is also reported by the Mereyala group to be successful with other 2-deoxy pyridylthio donors and other saccharide acceptors.



(17)

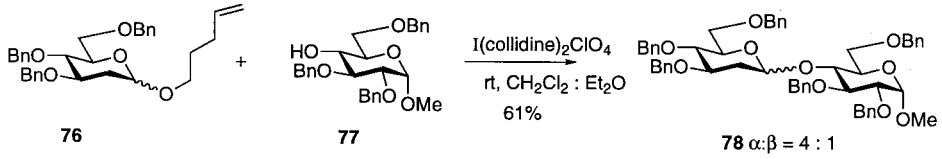
In another example of the use of the pyridine function to activate a leaving group, the pyridyl carboxylate of tribenzyl-2-deoxyglucose could be activated with either $Cu(OTf)_2$ in dichloromethane or $Sn(OTf)_2$ in acetonitrile to glycosylate both 3- and 6-hydroxy glucose derivatives (Eq. (18)).[30] It is interesting that the selectivity with the 3-hydroxyl acceptor is the same (92α:8β) with both catalysts, but the yields differ. On the other hand, the 6-hydroxyl acceptor gives essentially no selectivity with the Cu catalyst, but affords 80α:20β with the Sn reagent. When the donor protecting groups are switched from benzyl to acetate, the selectivity remains high with both catalysts and the 4-hydroxyl acceptor. The 6-hydroxyl acceptor shows degraded

selectivity with both catalysts.



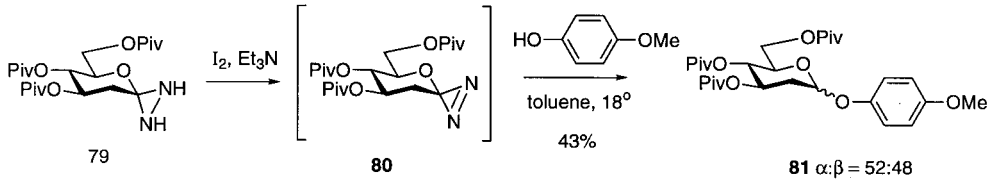
(18)

The Fraser–Reid *n*-pentenyl glycoside method has been used with tribenzyl-2-deoxyglucose as donor and three different glucose acceptors plus one galactose acceptor (Eq. (19)). The couplings took place in yields ranging from 40 to 77% and α:β selectivities ranging from 1:1 with a 6-hydroxyglucopyranose to 5:1 with the 3-hydroxy of diisopropylidene glucofuranose.[31]



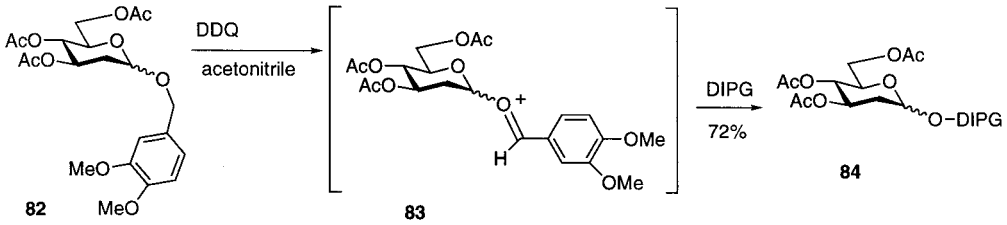
(19)

Vasella has developed anomeric diazirines (**80**) as unique agents for glycosyl transfer.[32] Although the chemistry for their preparation essentially rules out any general utility, their behavior is instructive in that they generate a 'hot' carbonium ion via protonation of the initially formed glycosyl carbene (Eq. (20)). This carbonium ion is not well solvated nor ion-paired nor influenced by the leaving group (N_2). In the 2-deoxy series, the diazirine has been coupled with two phenols and three alcohols to form α and β-glycosides averaging 52α:48β over 15 experiments with a range of 62:38 to 43:57.



(20)

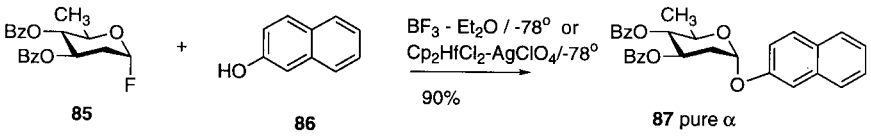
Another specialized method, limited to 2-deoxy sugars and due to Inanaga,[33] involves the DDQ oxidation of the dimethoxybenzyl glycoside (Eq. (21)). It is used as a 22:78 α:β mixture and forms two isomeric quinone methide-like oxonium ions which then react with the aglycone, either at the anomeric carbon or the benzylic carbon. With acetonitrile used as the preferred solvent for the reaction which is carried out at 80°C, octanol cholesterol, cyclohexanol and 1,2,3,4-diisopropylidene galactose (at 23°C) react to form α:β mixtures ranging from 1.2:1 to 2:1 in yields from a high of 96% to a low of 72%.



(21)

In the past decade, there has been a steady output of syntheses of aryl-*C*-glycosides (which are not the subject of this review). It is often the case that aryl-*O*-glycosides are obtained, either as intermediates to C-glycosides or as byproducts. For example, in the important Suzuki *C*-glycosidation method used for the synthesis of vineomycin B_2, low temperature reactions along with low-temperature quenching, of the fluoro olivose material with β-naphthol, afforded good yields of α-*O*-glycoside with both Suzuki catalysts Cp_2HfCl_2–$AgClO_4$ and $BF_3{\cdot}Et_2O$ (Eq. (22)). If the reaction was allowed to warm to 0°C before quenching, then mainly *C*-glycosides were obtained.[34] In closely related experiments, Suzuki reported the use of anomeric acetate glycosyl donors with the reactions requiring higher temperatures than with the fluoride donors. *C*-Glycosidation was always the major pathway with one exception.[35] The amino sugar donor combined with β-naphthol, using $BF_3{\cdot}Et_2O$ catalysis produced a 60% yield of *O*-glycoside (α:β=7:1) whereas $SnCl_4$ catalysis afforded a 43% yield of *O*-glycoside (α:β=27:1) (Eq. (23)). Evidently, the amino group complexed to the catalyst altered the reactivity of the anomeric carbon so that the expected O–C rearrangement was no longer favorable. Another example of a deactivated donor affording *O*- rather *C*-glycosidation under Suzuki conditions is the trifluoromethylolivose acetate. When it was treated with β-naphthol using

$BF_3{\cdot}Et_2O$ catalysis, an 87% yield of *O*-glycoside was obtained (α:β=3.4:1) (Eq. (24)).[36]



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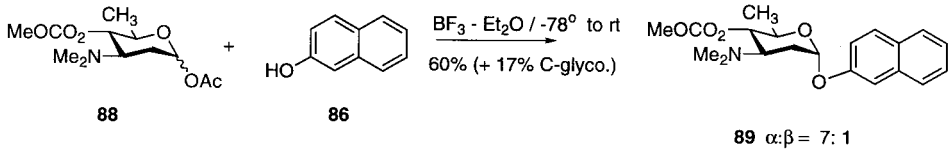

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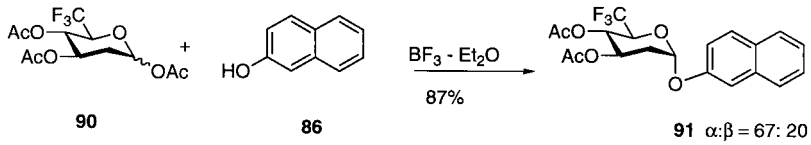
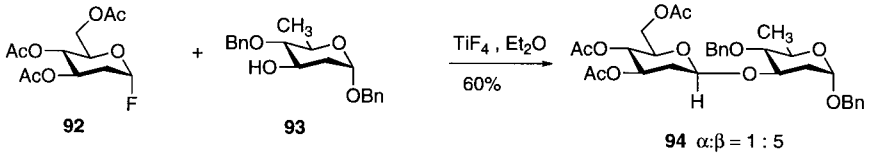


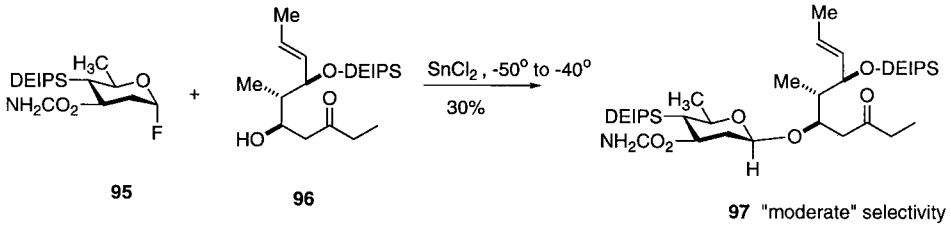
(24)

The Thiem group, pioneers in the 2-deoxyglycoside field, have described acetoxyglycosyl fluoride donors activated by TiF_4 catalysis.[37] In a striking reversal of stereoselectivity observed in ether solvent, the β-fluoro donor affords β-glycosides with 2 different glycosyl acceptors (α:β=1:4–5) whereas the α-fluoro donor affords α-glycoside (α:β=4–5:1). When the 6-substituent of the α-fluoro donor is changed from acetoxy to H, the β-selectivity vanishes (α:β=4–5:1) (Eq. (25)). These observations suggest an unusual double S_N2-like pathway in the β-examples where retention is observed.



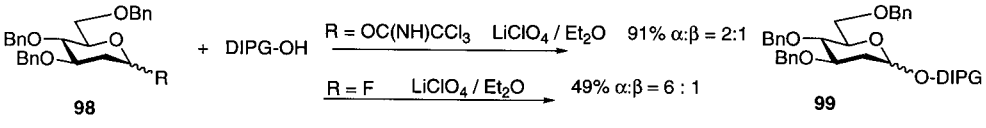
(25)

Another example of a 2,6-dideoxyglucosyl α-fluoro donor is found in pilot studies for a concanamycin A synthesis. Here, Mukayaima conditions, $SnCl_2$ in CH_2Cl_2 at −50 to −40°C, afforded a 30% yield of β-glycoside with 'moderate' selectivity (Eq. (26)), but the amount of α-glycoside was not stated by the authors.[38] Since the 3-protecting group here is diethyl isopropyl silyl and the 4-blocking group is carbamoyl compared to Thiem's acetoxys at both positions, a difference in pyranose ring conformation may account for the difference in selectivity.



(26)

The mildest catalysis yet recorded for glycosyl transfer using mainly 2,6-dideoxyfluoride donors and, in a few examples, a 2-deoxytrichloroacetimidate, is the $LiClO_4/Et_2O$ mixture reported by Waldmann (Eq. (27)). In this system α-glycosides are the principal products; and there is displayed an interesting anomer sensitivity to the nature of the acceptor. Also observed in the single comparison of leaving groups, the 2-deoxy tribenzylglucosyl fluoride afforded superior α-selectivity versus the 2-deoxytribenzylglucosyl trichloroacetimidate.[39] Nicolaou has used the fluoride donor of CBZvancosamine with catalysis by both $BF_3{\cdot}Et_2O$ and TMSOTf to produce a model vancosamine disaccharide in 89% yield (Eq. (28)) with α:β selectivity of 10:1.[40]



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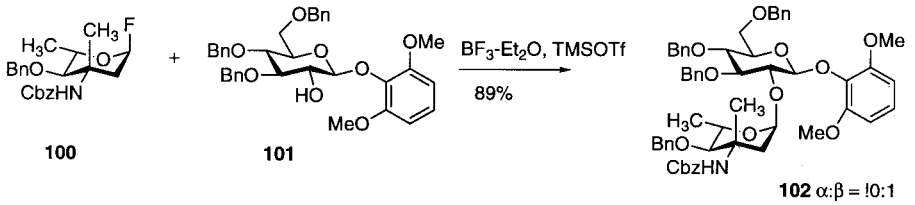
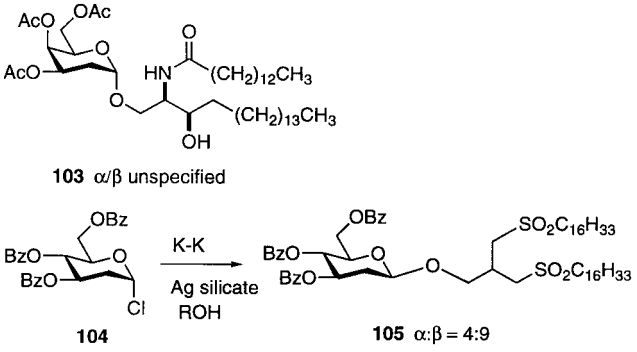


(28)

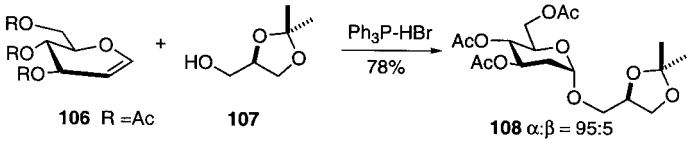
The antitumor 2-deoxygalactosyl ceramide **103** was prepared from the bromide donor plus ceramide using a modified Koenigs–Knorr procedure in unspecified yield and stereoselectivity.[41] The novel neoglycolipid **104** has also been prepared via Koenigs–Knorr chemistry.[42]

An important and general method for 2-deoxyglycosyl transfer is simply the acid-catalyzed activation of glycals to form an anomeric oxonium ion in the presence of an acceptor. For many years after the discovery of glycals by Fischer and Zach in 1913–1914, this acid-catalyzed step had been problematic because it was accompanied by varying degrees of Ferrier reaction where the oxygen substituent at C-3 is eliminated to form an allylic carbonium ion. In 1990, Falck and Mioskowski showed that the clever expedient of using triphenylphosphine hydrogen bromide suppressed the Ferrier reaction pathway, thus making the direct method of glycal activation general and useful.[43] The original disclosure described only gluco-configured material which gave useful α selectivity with a wide variety of acceptors (Eq. (29)). The Hunter group, in a followup, showed that the chemistry also gave α selectivity with galactal and β selectivity with allal. In an interesting aside, it was also shown, by use of deuterated catalyst, that the overall face-selectivity of addition to the glycal bond was *cis*, i.e. α protonation at C-2 with α-glycosides and β protonation at C-2 with β-glycosides.[44] Although the original report described 3 examples of moderate (>50%) yields of α-glycosides with phenol as the acceptor, later workers reported that when β-naphthol was the acceptor, the yields dropped precipitously because of the instability of the product α-glycosides.[45] The method has been applied to L-fucal diacetate and the benzenedimethanol acceptor to afford an α-glycoside in high yield with perfect selectivity.[46] The Falck–Mioskowski method has been applied by the Nicolaou group to prepare an α-glycoside starting material from a protected glucal with methyl glycolate in a peptide mimetic project.[47] The method has also been used by Paulsen with galactal triacetate and a four-fold excess of benzyl alcohol, producing the α-glycoside in 94% yield.[48]



(29)

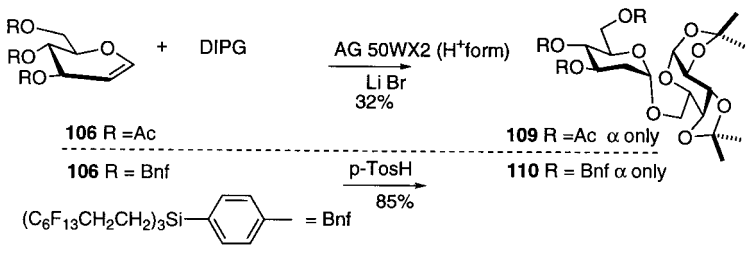
Contemporaneous with the Falck–Mioskowski work, Sabesan developed the use of anhydrous sulfonic acid resin as a proton catalyst for use with glycals. The resin is washed 10–15 times with equal volumes of anhydrous acetonitrile, the glycosylation is then run in acetonitrile solvent with the obligatory addition of lithium bromide along with the glycal donor and the alcohol acceptor. Five different acetylated glycal donors were tested along with a limited set of acceptors including diisopropylidene galactopyranose (Eq. (30)). Although the yields are not quite as good as in the Falck–Mioskowski route, the actual workup of the reaction is very simple since the catalyst is removed by filtration.[49] Russian chemists report the same method, including the required lithium bromide for the glycosylation of the 3-(secondary)hydroxyl of betulin, a triterpene. High yields of the α-glycosides derived from D-glucal, L-glucal and L-rhamnal are reported. Also described is the glycosylation of the C-28 (primary)hydroxyl located at the D–E ring fusion of the triterpene. The method has been applied to steroid aglycones such as cholesterol and methyl deoxycholate.[50]



(30)

Most simply, *p*-TosH and camphorsulfonic acid (CSA) have been reported to be useful catalysts in a few examples. Curran, in a development of his fluorous-3-phase technique for the simplification of reaction processing, described the *p*-TosH catalyzed coupling of a 'fluorous'-protected glucal with 10 equiv. of diisopropylidene galactopyranose to produce the protected

disaccharide in 85% crude yield from the fluorous solvent (Eq. (31)). The other materials remained in the organic solvent. The fluorous disaccharide was debenzylated and then acetylated to obtain a sample of the known disaccharide (for comparison purposes) in an overall 45% yield from starting glucal.[51] By using fluorous benzyl protecting groups and fluorinated solvents, the Curran group[7] was also able to obtain the same material following glycosylation with NIS and 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose followed by treatment with nBu$_3$SnH. Tosic acid also served to catalyze the addition of pyridine-2-thiol to 3,4-dibenzoyl glucal to obtain an anomeric mixture of thiopyridyl glucosides which were subsequently used as glycosyl donors in their own right (vide infra)[52] Danishefsky used CSA and a vancosamine-derived glycal to α-glycosylate the 2-OH of two phenyl glucosides which afforded the vancomycin models in 64% and 51% yield, respectively (Eq. (32)).[53] It is of interest that the iodonium-*sym*-collidine method was not useful with this glycal. Monneret has also described the addition of a 3-aminoglycal donor to a vancomycin-like model acceptor. In this case, reaction conditions required one full equivalent of trimethylsilyl triflate, initially at −45°C followed by quenching with Et$_3$N at room temperature which afforded an 85% yield of α-glycoside.[54] An acid-catalyzed method which may be limited to galactal triacetate involves refluxing a 5% glacial acetic acid solution in chlorobenzene with the glycal and four different phenolic acceptors to afford α-glycosides in 75–80% yield.[55] These conditions catalyze Ferrier rearrangement with triacetyl glucal.



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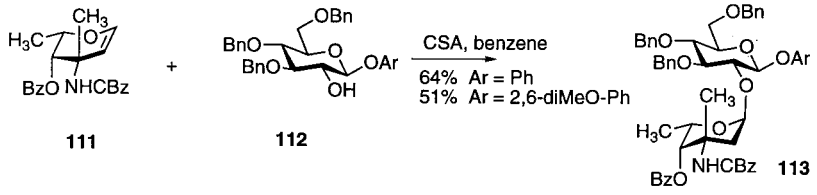
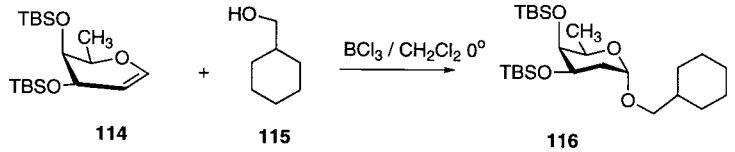


(32)

Boron trichloride and boron tribromide have been used as acid catalysts with TBDMS-protected glucal and galactal and some simple alcohol acceptors to afford α-glycosides in very high yields and excellent selectivity provided dichloromethane was used as solvent (Eq. (33)). The authors propose that the initial step of the process is reaction of the alcohol acceptor with the boron species to form a catalytic amount of HCl or HBr along with a borate ester species. They further show that the high yield of α-glycoside is due to the facile isomerization of β-glycoside product by the catalyst.[56] In a most unusual observation reported by the Thiem group (Eq. (34)), the glycal of the 3,4-diacetate of methyl glucuronate, when treated with BF$_3$–Et$_2$O catalyst and three simple hydroxy esters afforded 2-deoxy α-glycosides where the 3-acetoxy has been replaced by the hydroxy ester acceptor.[57] The reaction is not general.



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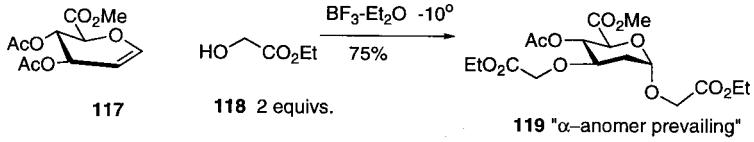
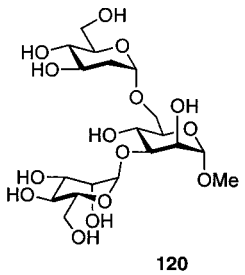




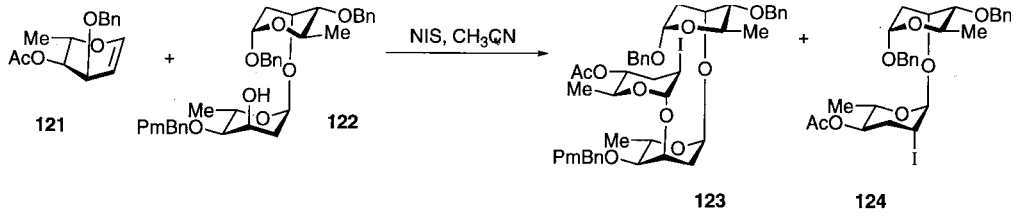
(34)

2.2. Halogen at C-2

Halogens have been found to add preferentially to the top face of glycals. Bridging halonium ions are proposed as intermediates in these additions. Attack on the intermediates by alcohol nucleophiles occurs exclusively at C-1, anti to the bridging species, giving rise to *trans* 2-halo-glycosides. The diastereomeric purity of the alkoxy halide is highly dependent on the extent to which the halogen can participate by bridging to help stabilize the developing anomeric oxocarbonium ion. In general, iodine gives better selectivity than bromine, which gives better selectivity than chlorine. The facile reductive removal of the halo group in the alkoxy halides allows for the easy formation of 2-deoxyglycosides.

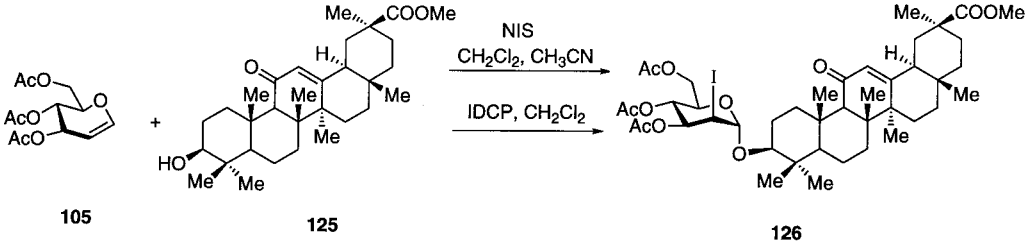
Glycals have been activated using a variety of halogen sources. The addition of *N*-iodosuccinimide (NIS) or iodonium-*sym*-collidine perchlorate (IDCP) to glycals in the presence of an acceptor has become a routine procedure for the synthesis of α linked disaccharides.

Deoxy analogs of methyl 3,6-di-*O*-α-D-mannopyranosyl-α-D-mannopyranosides **122** were synthesized for use as probes of the Concanavalin A binding site using the NIS method.[58] Regioselective coupling of tri-*O*-acetyl-D-glucal **105** with the 6-OH group of a disaccharide dihydroxy acceptor gave **122** in 83% yield. Thiem has used this methodology in the construction of the kijanimycin oligosaccharides (Eq. (35)).[59] Treatment of digitoxal (1.5 equiv.) with NIS (1.6 equiv.) and disaccharide **122** (1.0 equiv.) afforded the trisaccharide **123** in 24% yield, as well as, disaccharide by-product **124** in 24% yield and recovered starting materials. Catalytic hydrogenation (Pd/C) afforded the deoxy sugar. The formation of the disaccharide by-product was assumed to occur by the preferred nucleophilic attack of the interglycosidic oxygen of **122** instead of its 3′-OH group at the iodonium intermediate formed from **121**. The reduced nucleophilicity of the 3′-OH was attributed to unfavorable 1,3-diaxial interactions in the non-reducing end of **122**.



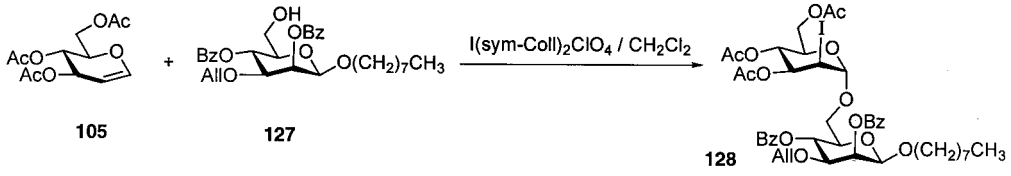
(35)

Triterpene 3-*O*-(2-deoxy-α-glycosides) have also been prepared by NIS promoted glycosylation of tri-*O*-acetyl-D-glucal **105** with two triterpenoids of licorice root as the alcohol components (Eq. (36)).[60] Equimolar amounts of sugar and triterpene were employed with 2 equiv. of NIS. Yields for the 2-iodo-saccharides ranged from 55 to 60%. Reduction to the 2-deoxyglycoside was accomplished using H_2 with a Pd/C catalyst in ethyl acetate.



(36)

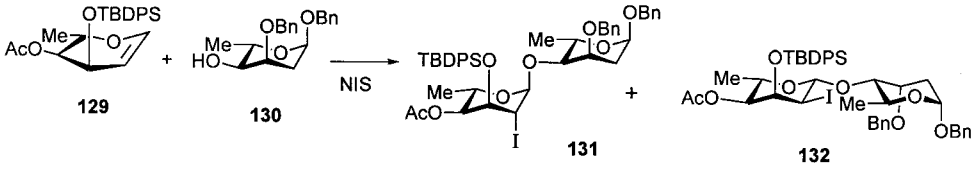
IDCP has also given good results as a promoter in the α-selective glycosylation of glycals. When used as a promoter in the reaction of tri-*O*-acetyl-D-glucal **105** with triterpene **125**, the 2-iodo-glycoside was isolated in 85% yield (Eq. (36)).[61] Paulsen used the IDCP protocol to prepare α-disaccharides in the synthesis of analogs of acceptor–inhibitors of *N*-acetylglucosaminyl transferases I and II (Eq. (37)).[62] The IDCP promoted glycosylation of glycals has also been used in an iterative sense for both the controlled[63] and combinatorial[64] synthesis of oligosaccharides.



(37)

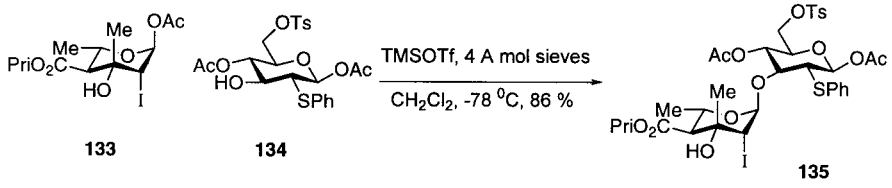
Although selectivities for the α-manno configured products are normally quite high using NIS or IDCP, β-glycosides were unexpectedly obtained in higher ratios than predicted (3:1, α:β) in the NIS glycosylation of 4-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-4-digitoxal with benzyl 3-*O*-benzyl-2,6-dideoxy-α-L-ribohexopyranoside (Eq. (38)).[65] When glycal (1 equiv.) and 4-OH sugar (1.25 equiv.) were treated with NIS (1.1 equiv.) in dry acetonitrile, **131** was isolated in 32% and **132** was

isolated as 11% from the crude reaction mixture. The unusual lack of selectivity observed was explained as a consequence of the steric bulk of the TBDPS group in the 3-position which prevented the acceptor from reacting with the allo-configured iodonium ion intermediate. Instead, attack at the altro-configured intermediate predominated, giving rise to the observed product distribution.



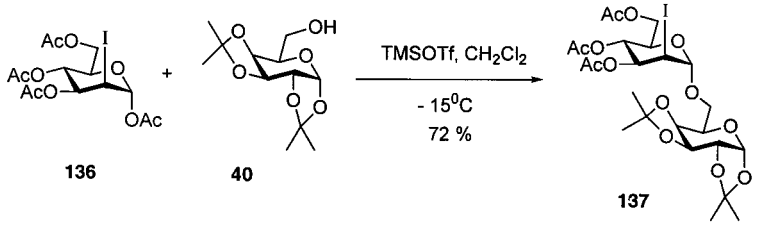
(38)

The addition of NIS and acetic acid, or I_2 and metal acetates in acetic acid, to glycals gives mixtures of *trans*-iodoacetates. The iodoacetates have also been successfully used as glycosyl donors. Roush[66] found that when he used NIS and acetic acid in a propionitrile solvent, at low temperatures, that predominately the α-manno iodoacetates (3–4:1 α-manno:β-gluco) were formed from glycals. A range of differentially protected glycals were examined (glucal, galactal, rhamnal and olivomycal). Iodoacetoxylation yields ranged from 48 to 90%. In most cases, selectivities for the α-manno configured iodoacetates were >9:1. Glycosylation reactions of slight excesses of the donor 1-*O*-acetyl-4-*O*-isobutyrl-2-iodo-α-L-olivomyacose **133** (1.0–1.5 equiv.) with 1 equiv. of one 6-OH sugar acceptor, three 3-OH sugar acceptors, one glycal 3-OH acceptor or one 4-OH sugar acceptor using TMSOTf (0.3–1.0 equiv) gave good yields of exclusively α-disaccharides (76–93%) (Eq. (39)). The lowest yield was obtained from the sterically hindered 4-OH acceptor, methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranose. Reduction of the 2′-deoxy-2′-iodoglycoside with Ph_3SnH in the presence of catalytic AIBN afforded 2′-deoxy disaccharide in 81% yield. The α-manno configured iodoacetate donors enabled Roush to prepare α-glycosides from sugars that were of poor or low reactivity in the direct NIS glycosylation protocol. This method was used in the total synthesis of the antibiotic Olivomycin A (to be discussed below.)[67] In some cases, even better selectivities for α-manno iodoacetates were obtained when Roush used a combination of ceric ammonium nitrate (CAN) and sodium iodide in acetic acid/acetonitrile (>9:1).[68]



(39)

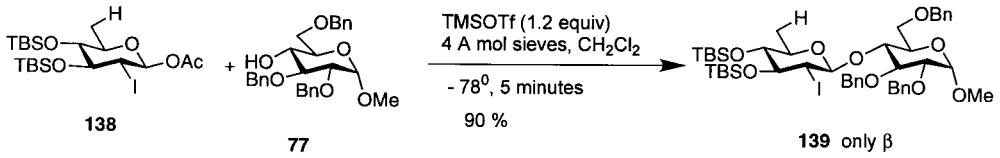
Lafont and coworkers also achieved high levels of selectivity for the α-manno configured iodoacetates using a mixture of I_2 and $Cu(OAc)_2$ in AcOH.[69] The glycals reacted were 3,4,6-tri-*O*-acetyl-D-glucal and 3,4-di-*O*-acetyl-L-rhamnal. The selectivities for the 1,2-*trans*-diaxial iodoacetates were 11α:1β and 4α:1β, respectively. Glycosylation reactions (Eq. (40)) of the iodoacetate donors were carried out with slight excesses (1.25–1.4 equiv.) of the following acceptors: 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranose and 1,6-anhydro-2,3-*O*-isopropylidene-β-D-mannopyranose. Stoichiometric amounts of TMSOTf were employed. Exclusively α-disaccharides were obtained in 72, 73 and 80% yield, respectively. Reduction with nBu$_3$SnH/AIBN gave good yields of 2-deoxysaccharides.



(40)

Equatorially disposed iodoacetate donors have also been prepared and used as β-selective glycosyl donors. Kirschning reported the formation of these compounds in good selectivities (α:β, 1:10) from the iodoacetoxylation reactions of glycals bearing bulky silyl ether groups with hypervalent iodine reagents.[70] This methodology was used to prepare the repeating trisaccharide unit of the antibiotic Landomycin A (to be discussed below). These donors have also been prepared selectively by reaction of the known 1,6-anhydro-2-iodo-D-glucose with trifluoroacetic anhydride and acetic acid (82–86%).[71] These donors, when treated with TMSOTf, at −78°C in the presence of excess acceptor, gave excellent yields for 2-iodo-β-gluco-disaccharides (62–93%). With less reactive donors, 2 equiv. of donor were used with 1 equiv. of acceptor; whereas more reactive donors were used as limiting reagents, 0.05–0.5 equiv. of promoter were used. In many instances, the β-disaccharide was obtained exclusively (Eq. (41)). The lowest ratio detected was 9:1 β:α. The best results were obtained when the glycal precursor lacked oxygenation at C-6, or when it was bis-silylated and could readily exist in a twist boat conformation. Subsequent easy removal of the 2-iodo substituent with nBu$_3$SnH, afforded the 2-deoxy-β-disaccharides. All the other glycosyl donors studied that adopt the normal $^4C_1$ conformation and/or have deactivating heteroatom substituents at C-6, required a higher temperature. This

reduced the product yields for acid-sensitive precursors. Conversion of the acetates to 2-deoxy-2-iodo- and 2-deoxy-2-bromo-α-glucopyranosyl trichloroacetimidates afforded superior donors under these conditions, giving high yields of 2-deoxy-2-halo-β-disaccharides at lower temperatures (71–93%; β:α 10:1 to >99:1).[72]



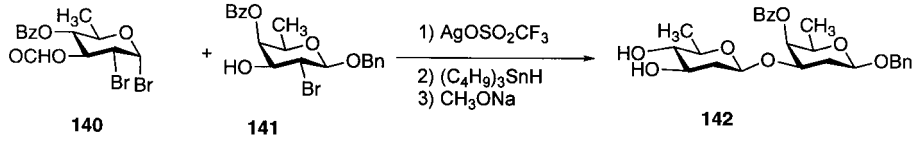
(41)

2-Bromo-2-deoxy-glycosyl bromides have also been used as β-selective donors.[73] These donors are prepared by the action of dibromomethyl methyl ether (DBE) on protected sugars. Treatment of the mixture of predominately *cis* α-1,2-dibromide with either silver triflate or silver carbonate affords in modest selectivities (3:1–10:1, β:α) 2-bromo-2-deoxy-β-glycosides (Eq. (42)). The halogen can then be removed under reductive conditions (nBu$_3$SnH/AIBN). This method was used to prepare the C–D–E trisaccharides of mithramycin and aureolic acid and the D–B disaccharide unit of kijanimicin.

2.3. Sulfur and selenium at C-2

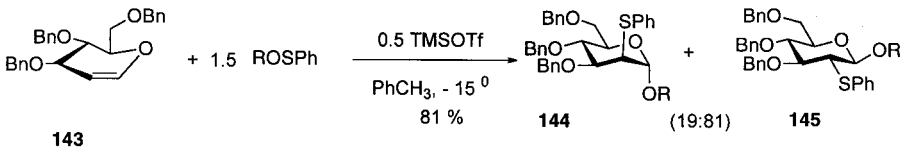
Electrophilic sulfur and selenium species in the presence of alcohols add to the double bonds of glycals in a *trans* fashion to give glycosides. The face-selectivity of approach may be influenced by a variety of factors including the conformation of the reacting glycal and the nature of the substituents on the glycal. In addition, different face-selective approaches are observed for the two electophiles.

For glycals that exist in the normal $^4H_5$ conformation, sulfonium species have been observed to attack predominately from below the plane of the glycal. Attack by the alcohol nucleophile is frequently *trans* to the sulfur substituent. Episulfonium ion intermediates have been proposed to account for the observed product distributions. The good selectivities obtained from electrophilic sulfur reagents has given rise to their extensive use for the preparation of 2-deoxy-2-thio-β-glycosides. The sulfur group at C-2 is easily removed using either tin hydride based reagents or with Raney Nickel and H_2 to afford the 2-deoxy-β-glycosides.

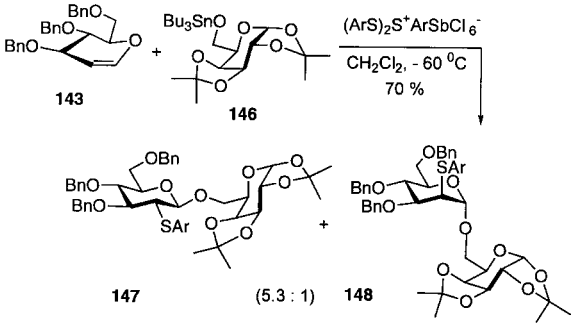


(42)

Ogawa and Ito used preformed sulfenate esters of alcohols for the direct addition to glycals (Eq. (43)).[74] Mixtures of α-manno and β-gluco-2-deoxy-2-thiophenyl glycosides were obtained from this procedure. A variety of substituted glycals were studied with the sulfenate esters of methanol, isopropanol, methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside and benzyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside. The glycosylation reactions were optimized by varying the reaction conditions: solvent, catalyst, temperature, reaction time and molar quantities. Yields ranged from 43 to 99% and selectivities ranged from 52:48 to 81:19 for the β and α products, respectively. TMSOTf proved to be the most effective catalyst for these reactions. An excess of sulfenate ester (1.5 equiv.) was used. The selectivities for the products obtained varied considerably with the glucal protecting groups. Tri-*O*-acetyl-D-glucal **105** gave nearly 1:1 mixtures of α:β anomers in nearly every case, whereas, tri-*O*-benzyl-D-glucal showed an appreciable level of selectivity giving β-anomers as major products in 1,2-dichloroethane (73:27) or toluene (81:19). The reaction of tri-*O*-benzyl-D-galactal was also examined. With the methyl sulfenate acceptor, 0.1 equiv. of TMSOTf in dichloroethane at −15°C, a lower *trans* specificity was observed (80:20; *trans*:*cis*) after a 30 min reaction time. The diastereofacial selectivity in the addition of sulfur to the equatorial plane was still high (88:12) suggesting that steric factors between the C-4 benzyloxy group and the sulfenate ester play a major role in the stereochemical outcome of these reactions. Franck and coworkers saw similar trends when arylbis(arylthio) sulfonium salts were used to activate glycals for attack with carbohydrate-derived tin ethers (Eq. (44)).[75] In addition to varying factors such as glycal protecting groups, the nature of the arylthio group and the type of glycal used were directly compared. Glycosylations were run with methanol, isopropanol and *t*-amyl alcohol, as well as with, the tin ethers of 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose, 1,2,5,6-di-*O*-isopropylidene-α-D-glucopyranose, a racemic acyloin and various phenols. For tri-*O*-benzyl-D-glucal and the phenyl bis(phenylthio)sulfonium salt with these alcohols and tin ethers, yields ranged from 83 to 43%. The selectivities for the *trans* products varied from a low of 2.7:1 (β:α) for isopropanol to only β-diastereoisomers for the racemic acyloin. Overall, the *p*-tolyl sulfonium salt gave the best β selectivity with tri-*O*-benzyl-D-glucal. The nature of the glycal was also found to influence the facial selectivity of attack of the sulfur electrophile. Axial alkoxy groups were found to direct the electrophile to the opposite face of the molecule. Steric factors in the alcohol, sulfonium salt and glycal all contributed to the observed stereoselectivities. The resulting 2-deoxy-2-thiophenyl-glycosides were then treated with Ra Ni to afford 2-deoxy-β-glycosides. This approach was used to construct the C–D rings of an aureolic acid analog.

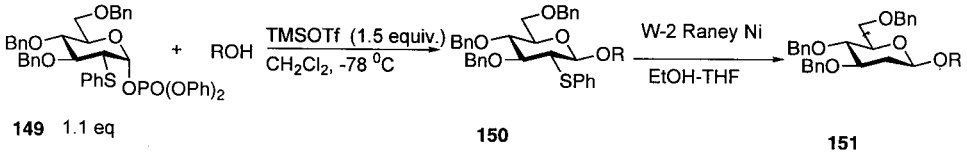


(43)



(44)

Glycosyl donors derived from the 2-deoxy-2-thiophenyl-glycosyl chlorides have also been utilized to prepare equatorially linked saccharides. The facile hydrolysis of the glycosyl chlorides to reducing sugars has led to the preparation of anomeric *N*,*N*,*N*′,*N*′-tetramethylphosphoroamidates. The phosphoroamidate donors proved to be quite reactive with a variety of alcohols.[76] Glycosides were prepared from two primary and three secondary hydroxy sugar acceptors, a steroidal alcohol, a racemic acyloin, and two phenols. A slight excess of donor (1.1 equiv.) were reacted with 1 equiv. of acceptor and 1.5 equiv. of TMSOTf. The reaction of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside with the α-gluco donor **149** gave a 95% yield of glycosides with >99:1 selectivity for the β-anomer (Eq. (45)). In general, the proportion of β-products was very high (89:1 to >99:1). Yields ranged from a low of 65% for cholesterol to 97% for the racemic acyloin. Treatment with Raney Nickel gave the desired 2-deoxy products in good yields (42–76%). Recently, Roush has used a similar approach to construct the 2-deoxy-β-glycosidic linkages found in the aureolic acid family of antibiotics. Addition of phenylsulfenylchloride to protected glycals, then hydrolysis of the anomeric chlorides using silver carbonate afforded the reducing sugars. In each case, a mixture of anomeric trichloroacetimidates was then formed which reacted as excellent glycosyl donors to suitably protected glycal acceptors when treated with TMSOTf (Eq. (46)).[77] Coupling of a preformed D–E disaccharide trichloroacetimidate with the C sugar-aglycone afforded a 78% yield of the olivomycin C–D–E aglycon complex (to be described below).



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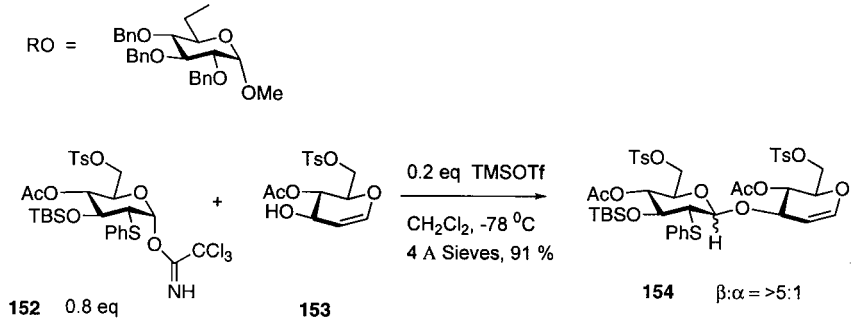
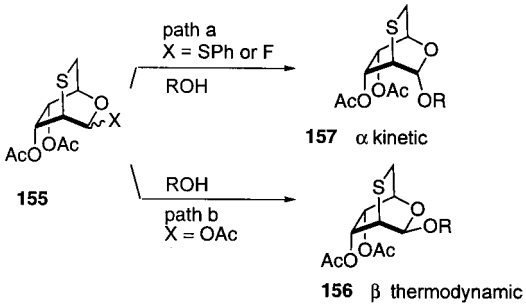


(46)

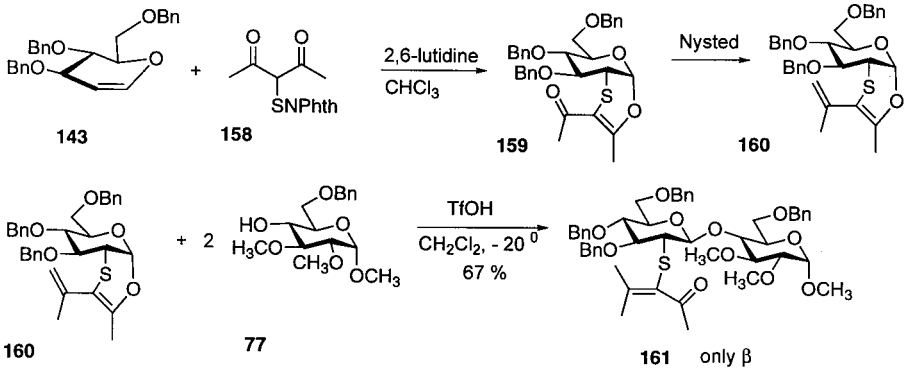
Glycosides of 2,6-dideoxysugars have also been prepared using a temporary bridged sulfur tether at the C-2 position. Using 2,6-anhydro-2-thio sugars, both α- and β-2-thioglycosides could be accessed selectively for a variety of simple primary, secondary and tertiary alcohols.[78] When the anomeric group was a fluoride or a thiophenyl substituent, α-glycosides were obtained in high selectivity (>95:5) when activated in the presence of an acceptor molecule. When the anomeric group was an acetate, high yields of the β-glycoside were obtained (Eq. (47)). For the glycosyl fluoride, the highest yields of α-glycoside (97%) were obtained using 2 equiv. of cyclohexylmethanol with 2.2 equiv. of a 1:1 mixture of $SnCl_2/AgClO_4$. The selectivity for this reaction was 97:3 (α:β). For the thiophenyl glycosyl donor coupled to the same acceptor (1.5 equiv.), MeOTf

(5.0 equiv.) activation afforded a 92% yield of only the α-glycoside. NBS activation (1.1 equiv.) also gave outstanding α-selectivity in high yield (94%). An interesting trend was observed for the acetate donors, whereas when 2 equiv. of acceptor and 1 equiv. of donor were treated with 1.1 equiv. of TMSOTf in dichloromethane, an 89% yield of predominately β isomer was obtained (2:98; α:β). When the same molar ratios were used in THF, an 89% yield of mainly the α isomer was found (96:4; α:β). Deactivation of the donors could be accomplished by oxidation of the bridging sulfur to the sulfoxide. Conversion of the saccharides to 2,6-dideoxy sugars could be conducted either by hydrogenolysis (Ra Ni) or by using Bu_3SnH/AIBN. This method was used in the synthesis of Erythromycin A and in the synthesis of the Olivomycin A trisaccharide.[79]



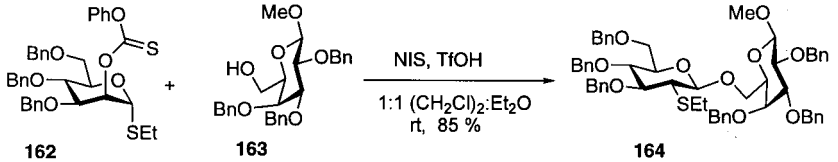
(47)

Bicyclic glycosyl donors appended with sulfur at C-2 have been prepared by the cycloaddition reaction of glycals with oxothioheterodienes.[80] From tri-*O*-benzyl-D-glucal, the α-gluco adduct **159** is obtained in good yield and stereoselectivity (80%; 16:1 α-gluco:β-manno). The direct activation of the α-gluco adduct with acid catalysts leads to the sluggish formation of β-glycosides; whereas the minor β-manno adduct, formed from the cycloaddition, was smoothly converted to α-glycosides.[81] Methylenation of the bicylic α-gluco donor with Nysted Reagent enhanced its reactivity. Glycosylations were successfully performed on the modified α-gluco cycloadducts **160** with triflic acid or triflic acid/nBu_4NOTf to give almost exclusively β-glycosides with a variety of acceptor molecules (Eq. (48)).[82] The yields of glycosides obtained ranged from 74 to 57% for most alcohols and sugar acceptors studied. The procedure was also effective for β-naphthol and for a racemic acyloin. Desulfurization was accomplished with Raney Nickel (35–95%). Alternately, β-gluco adducts modified by reduction and acetylation were also useful glycosyl donors, and over time, led to the formation of α-glycosides, presumably due to equilibration processes between the products and starting donor.[83]



(48)

Ethyl (phenyl)-1-thioglycosides having at C-2 a *trans* oriented phenoxythiocarbonyl group have been shown to be useful precursors for 2-deoxy-α- and β-glycosides (Eq. (49)).[84] α-Manno configured 1-thiopyranosides are converted exclusively to β-gluco-2-thioglycosides in the presence of various sugar acceptors, whereas the β-gluco donors give exclusively α-manno-2-thioglycosides. Because of the formation of completely inverted products, intermediate episulfonium ions were proposed as intermediates in these glycosylation reactions. Three sugar acceptors were used: methyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside, methyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside. A slight excess of donor (1.2 equiv) and catalytic NIS/TfOH were used. Yields of the 2-deoxy-2-thioglycosides ranged from 61% (for the less reactive axial 4-OH in the galactopyranose acceptor) to 85% for the primary hydroxyl donor. Only the inverted, 1,2-*trans* products were obtained. Nicolaou has also reported a similar 1,2-migration of anomeric thiophenyl groups in sugars containing a *trans* configured free hydroxyl group at C-2. When treated with 1.5 equiv. of DAST, 2-thiophenyl glycosyl fluorides were obtained which were used as donors in the preparation of the 2-thiophenyl precursors for the B–C sugar rings of the antibiotic Everninomicin (Eq. (50)).[85]



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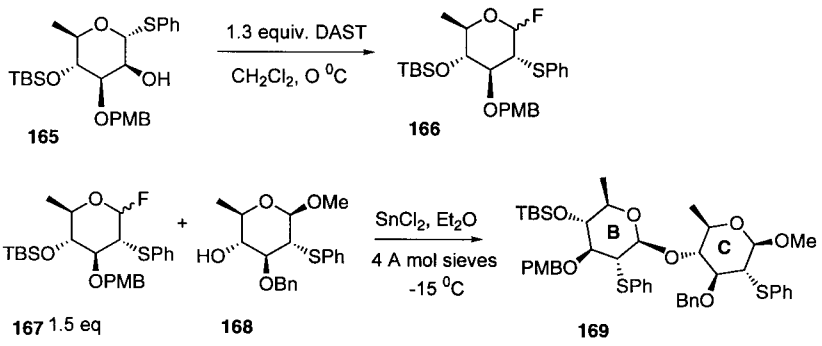


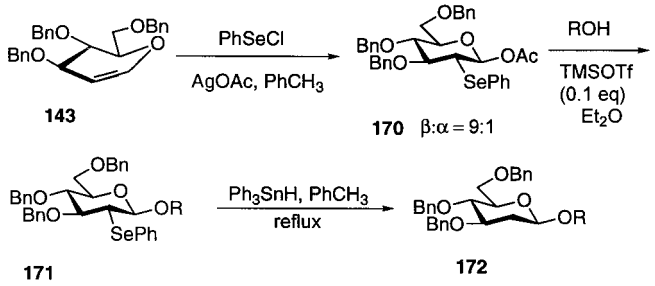
(50)

Selenium electrophiles add predominately above the plane to glycals in the $^4H_5$ conformation. In the direct glycosylation method with glucal derivatives, this leads to 2-deoxy-2-selenophenyl-glycosides with the α-manno configuration. Deselenylation with tin hydride based reagents gives the 2-deoxy-α-glycosides. Using this approach, the disaccharide moiety of Avermectin A_{2b} was prepared (see Eq. (75) below).[86] β-Linked 2-deoxy-disaccharides are accessible via the 2-deoxy-2-selonophenyl-glucosyl acetates. Addition of phenylselenylchloride and silver acetate in toluene to tri-*O*-benzyl-D-glucal affords an 81% yield of a mixture of α-manno and β-gluco diastereoisomers (9:1 β:α) (Eq. (51)). For other glycals studied, the selectivity of addition of reagents was found to be highly dependent on the nature of the glycal protecting groups. For example, benzoylation at position 4 was found to favor an α-selective addition to the glycal. Treatment of 4-*O*-benzoyl-3-*O*-tertbutyldimethylsilyl D-glucal with 1.3 equiv. of PhSeCl and 1.5 equiv. of silver acetate gave a 10:1 mixture of β-gluco to α-manno selenoacetates. Disaccharides were prepared by treatment of the preformed donors with 0.8 equiv. of acceptor and catalytic TMSOTf (0.1 equiv.). In some instances, selectivites of >10:1 in favor of the β-gluco isomers were obtained. The yields reported were generally greater than 75%.[87] Further, systematic study by Roush supported the role of the C-4 and C-6 glycal substituents on the selectivity of selenophenyl and thiophenyl electrophiles to glycals.[88] Whereas the C-6 group controlled the conformational properties of the glycal, a polar C-4 substituent was proposed to stabilize episelenonium intermediates. Roush also observed substantial configurational instability in the 2-selenophenyl acetate donors and the formation of up to 50% of the undesired α-glycoside from this protocol.

Nicolaou and coworkers used polymer supported selenium reagents for the solid-phase synthesis of 2-deoxy-glycosides. When a selenylbromide polystyrene supported resin was reacted with tri-*O*-benzyl-D-glucal then with added sugar acceptor (1.0 equiv.), α-linked disaccharides were obtained selectively (5:1 α:β for benzyl alcohol; 8:1 for methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside). On the other hand, when the resin was coated with a phthalimidoselenyl functionality and reacted with glycal and acceptor molecules, β-linked disaccharides were obtained selectively (1:5 α:β for benzyl alcohol; 1:1 for methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside). Cleavage of the resin bound selenyl group could be carried out using nBu$_3$SnH and AIBN.[89]

2.4. Oxygen at C-2

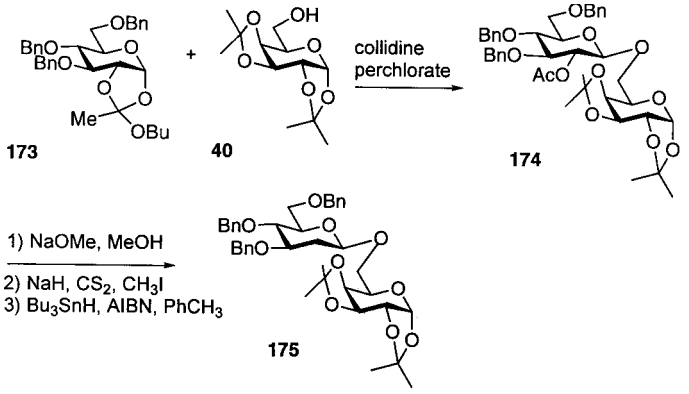
Fully oxygenated glycosyl donors have been frequently used to prepare 2-deoxy-glycosides. The oxygen moiety is readily converted to a stable free radical precursor that undergoes facile reductive cleavage. Both 2-deoxy-α and 2-deoxy-β-glycosides have been prepared by this route.



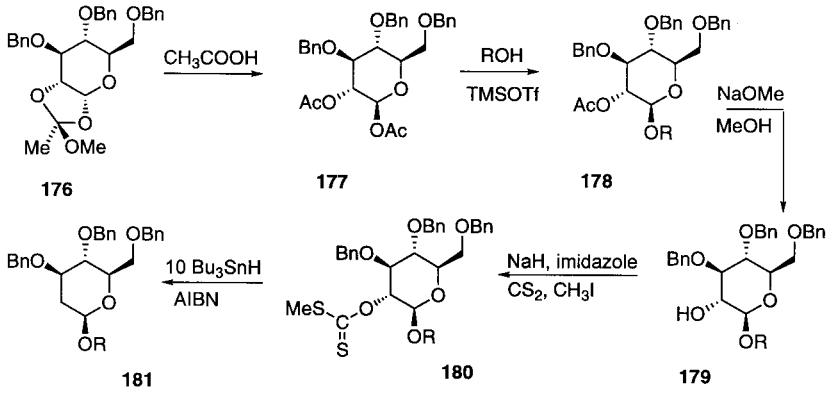
(51)

The conversion of C-2 oxygen to thiocarbonate esters that undergo reductive cleavage with tri-*n*-butyl tin hydride and AIBN has been often used to form 2-deoxyglycosides. Frequently, orthoesters or 2-acetoxy sugar donor precursors are employed owing to the participatory nature of these substituents and the high β-selectivity realized from the gluco derivatives following glycosylation. For example, treatment of 1,2-*t*-butylorthoacetate and 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose in the presence of collidine perchlorate afforded a 41% yield of β-disaccharide. Conversion of the 2-acetoxy-glycoside into the thiocarbonate, followed by treatment with tri-*n*-butyl tin hydride and AIBN, afforded the 2-deoxy-β-glycoside (Eq. (52)).[90] Sinay and coworkers prepared 2-acetyl β-hexopyranosyl acetates from their corresponding orthoesters by treatment with acetic acid. Glycosylation of the anomeric acetates with alcohols and TMSOTf gave good yields of β-disaccharides (75–90%).

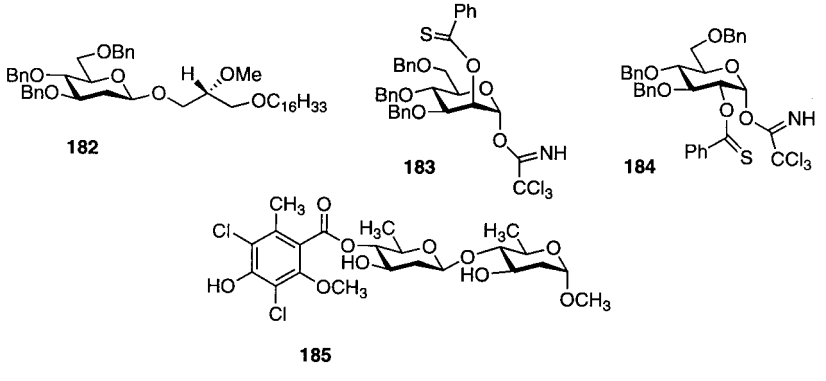
Three types of donors were used and five different sugar acceptors were coupled. Equimolar quantities of reagents were employed in these reactions. Zemplen deacylation of the 2-acetoxy functionalities, followed by conversion to the thiocarbonate esters and treatment with tri-*n*-butyl tin hydride gave yields of 75–90% of 2-deoxy-β-disaccharides (Eq. (53)).[91] Recently, a similar approach has been used to synthesize antitumor ether glycolipid **182**. An anomeric trichloroacetimidate donor was prepared from 2-acetoxy-β-glucopyranosylacetate by hydrolysis followed by treatment with trichloroacetonitrile and potassium carbonate. Using a catalytic amount of TMSOTf (0.035 equiv.) and 1.1 equiv. of 1-*O*-hexadecyl-2-*O*-methyl-sn-glycerol, a 76% yield of pure β-glycoside was obtained. Hydrolysis of the 2-acetoxy moiety, conversion of the alcohol to the xanthate and deoxygenation with tributyl tin hydride occurred in 94% yield to afford the corresponding 2-deoxy-β-glycoside.[92] Schmidt obtained exclusively α-linked disaccharides from *O*-(2-*O*-thiobenzoyl-mannopyranosyl) trichloroacetimidates **183**, whereas the β-linked disaccharides were the sole products from the corresponding *O*-(2-*O*-thiobenzoyl-gluco-pyranosyl) trichloroacetimidates **184**.Compound **183** was prepared in several steps from allyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranose. Compound **184** was synthesized from 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-glucopyranose. Radical initiated deoxygenation with Bu_3SnH/AIBN directly furnished 2-deoxyglycosides.[93] The A–B–C subunit **185** of the antibiotics flambamycin, curamycin and avilamycin, which includes a 2,6-dideoxy-β-linkage between the B and C components was prepared using a 2-acetoxy-6-deoxyglycosylbromide donor (2.5 equiv.) for ring B, activated with Helferich catalyst (mercury (II) cyanide) in the presence of 1 equivalent of methyl 3-*O*-benzyl-2,6-dideoxy-α-D-glucopyranose (78% yield). The B ring 2-acetate was subsequently removed via conversion to a phenyl thiocarbonate and tin hydride reduction.[94]



173 40 174 175 (52)

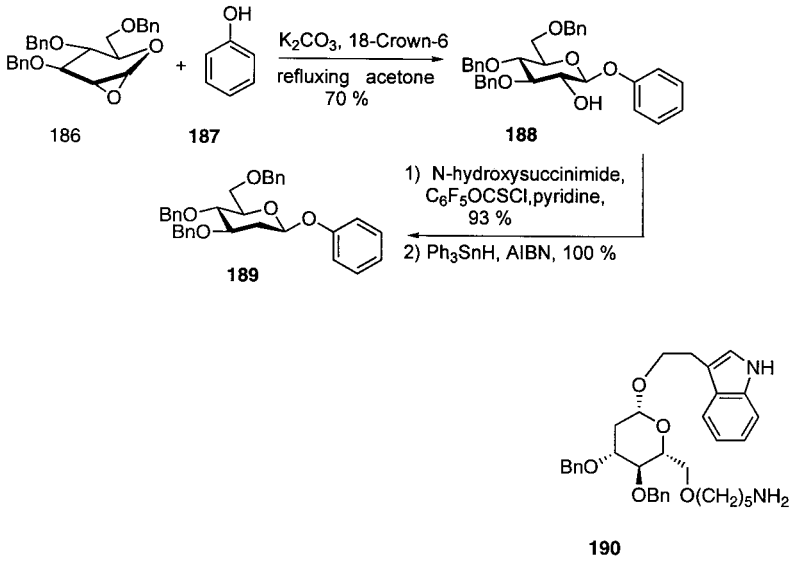


176 177 178 179 180 181 (53)



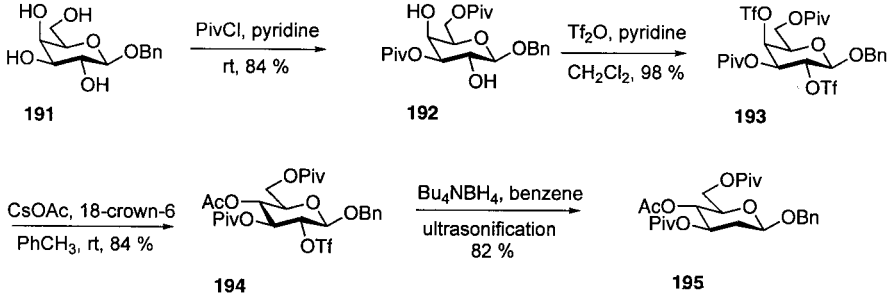
182 183 184 185

Glycals, when treated with 3,3-dimethyldioxirane, give rise to α-epoxides in high yields. Treatment of the glycal epoxides with zinc chloride in the presence of alcohol acceptors gives modest to good yields of β-linked disaccharides. Subsequent conversion of the C-2 hydroxyl groups to the thiocarbonates followed by deoxygenation using the Barton protocol provides 2-deoxy-β-glycosides. This approach was used to synthesize three different 2-deoxy-disaccharides from 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside and 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose, 4,6-di-*O*-benzyl-D-galactal and 4,6-*O*-benzylidene-D-glucal[95] Whereas 1 equiv. of the epoxide was added, 1.5 equiv. of both the acceptor and promoter were required. By treating the epoxide with phenolate anions, the difficult to prepare phenolic-*O*-glycosides were also obtained stereoselectively in modest to good yields (42–86%) (Eq. (54)). Hirschmann and coworkers[96] used a similar epoxidation, deoxygenation sequence to construct 2-deoxy-gluco scaffolds containing non-peptide peptidomimetics such as **190**, a mimic of the peptide hormone somatostatin.



186 187 188 189 190 (54)

Benzyl glycosides of 2,4-bis-*O*-trifluoromethanesulfonate protected galactose derivatives have been selectively manipulated to form benzyl 2-deoxy-β-glucosides. The C-4 axial triflate group is selectively reacted with cesium salts to afford the equatorial gluco acetate or free hydroxy group at C-4. Reduction of the 2-*O*-triflate with Bu_4NBH_4, gives the 2-deoxy-benzylglucoside in good yield (82%) (Eq. (55)).[97]

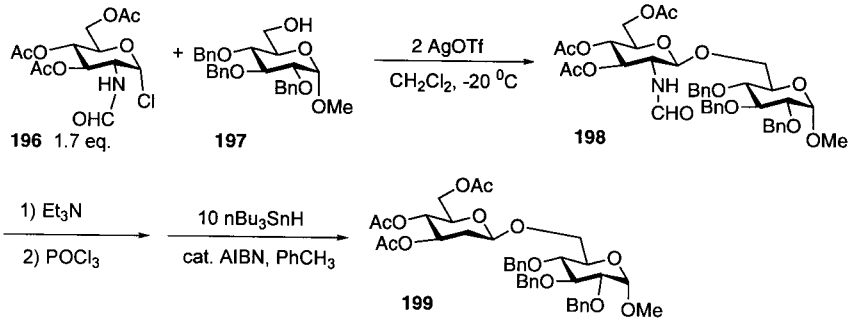


191 192 193 194 195 (55)

2.5. Nitrogen at C-2

β-Glycosides have been prepared in modest yields from various derivatives of *N*-formylglucosamine. Intermediate oxazolinium ions are proposed to give rise to a high level of β-selectivity in these glycosylation reactions. When the anomeric group was a β-acetate or an α-trichloroacetimidate, activation with TMSOTf in the presence of a sugar acceptor lead to predominately β-disaccharides. For the α-chloride, activation was effected with silver or tin triflate. In all cases, 1 equiv. of alcohol acceptor was reacted with an excess of donor (2 equiv. of acetate, 1.7 equiv. of chloride, 1.2 equiv. of imidate) and an excess of promoter (acetate: 3 equiv. of TMSOTf; chloride: 2 equiv. of AgOTf; imidate: 1.2 equiv. of TMSOTf). For all of the donors, good yields of β-disaccharides were obtained when the acceptor molecule was a primary alcohol (97–64%). Lower yields of the desired product were obtained with secondary alcohol acceptors (64–15%). With these secondary alcohol acceptors, the formation of the isomeric α-disaccharides was competitive. The resulting β-disaccharides were then smoothly deaminated into the corresponding 2′-deoxy-β-disaccharides by dehydration to the 2-deoxy-2-isocyano derivatives followed

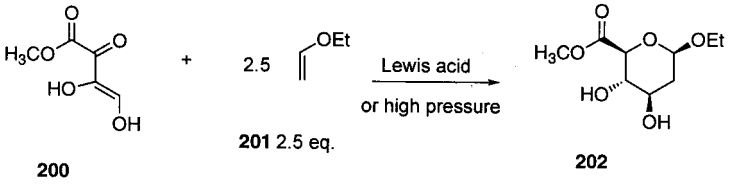
by reduction with tributylstannane (96–74% yield) (Eq. (56)).[80]



(56)

2.6. 2-Deoxyglycosides by cycloaddition reactions

Simple glycosides have been prepared by the inverse electron demand [4+2] cycloaddition reaction of vinyl ethers with heterodienes. Boger and Robarge[98] reacted β,γ-unsaturated α-keto esters with electron rich dienophiles to prepare a variety of racemic ethyl and benzyl glycosides (Eq. (57)). Optimal yields for the cycloaddition reactions were obtained using 2.5 equiv. of alkene and 13 kbar of pressure at room temperature (82–49%; 5.7:1 to >45:1 *endo*/*exo*). The adducts derived from ethyl vinyl ether could then be reduced to afford either 2-deoxy or 2,4-dideoxymannopyranosides. Similarly, heterodienes derived from L-ascorbic acid when reacted with ethyl vinyl ether afforded preferentially the *endo*-adducts with the α-L-erythro isomers predominating (Eq. (58)).[99] An excess of dienophile is employed as the solvent in these reactions which were carried out in a sealed tube at 75°C. The resulting adducts could be converted to ethyl 3,4,6-tri-*O*-acetyl-2-deoxypyranosides in 8 additional steps. Pyranone **208**, which was prepared by the [4+2] cycloaddition of acylketene with butyl vinyl ether, was also converted in a multistep approach to the arabino hexopyranosides olivoside and oleandroside and into the branched sugars olivomycoside and chromoside B (Eq. (59)).[100]



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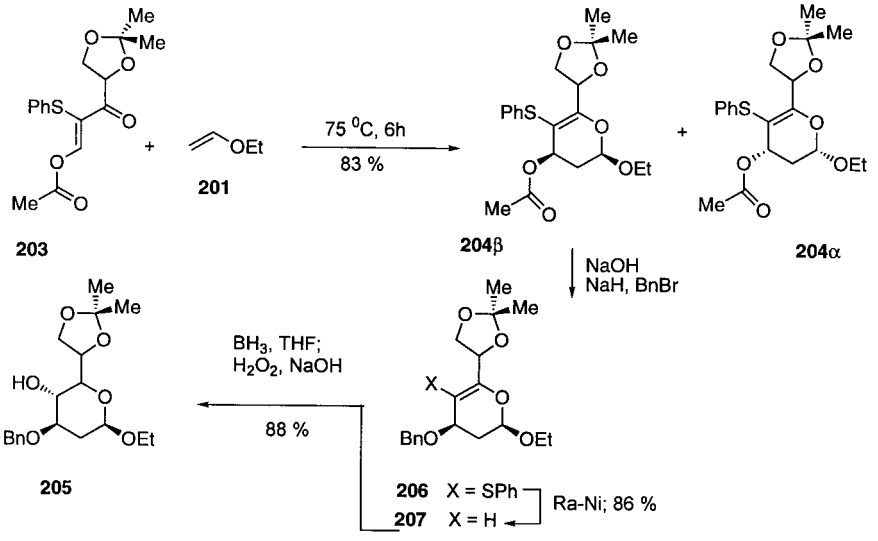

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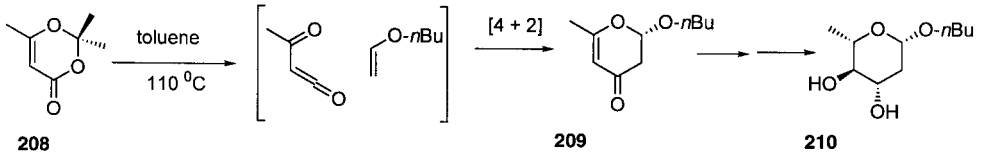
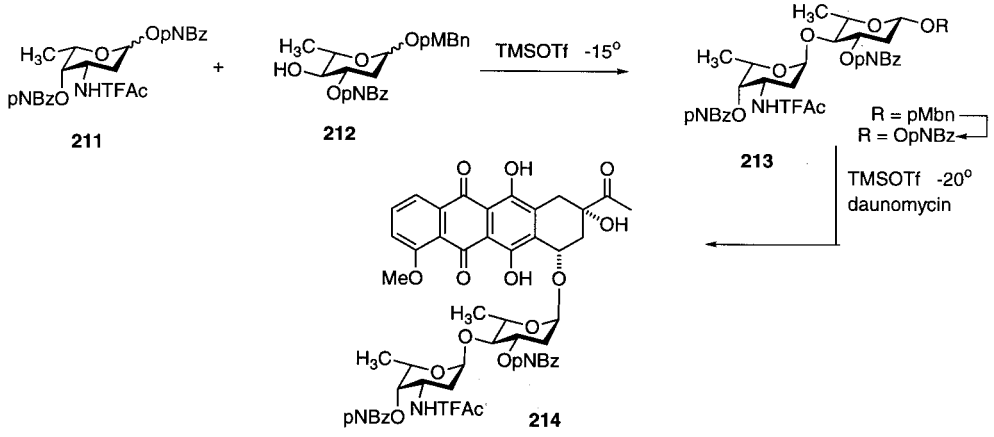


(59)

2.7. Applications to natural products

The anthracycline antibiotics have continued to provide a target for the application of 2-deoxyglycosyl transfer methods. A daunorubicin disaccharide derivative with reportedly enhanced antitumor activity has been prepared via two TMSOTf couplings. First, daunosamine as its anomeric *p*-nitrobenzoate was α-linked to the 3-OH of L-2-deoxyrhamnose in 79% yield. This disaccharide, activated as its *p*-nitrobenzoate was then similarly coupled to both daunomycin and its 4-demethoxy analog in 60 and 57% yield, respectively (Eq. (60)). The same sequence was carried out with L-2-deoxyfucose replacing rhamnose.[101] Kolar has reported the activation of the anthracycline-relevant 6-deoxyglycals with TMSOTf–triethylamine in coupling with the 4-OH of daunosamine in excellent yields (Eq. (61)). Similarly, trisaccharides could be obtained by linking a deblocked 4′-OH of the product dissaccharide to a second glycal donor with the same catalytic conditions.[102] TMSOTf catalysis was also exploited by Kolar for rhodomycin syntheses. Thus, the 1-OTBDMS derivatives of various 2,6-dideoxy sugars were smoothly coupled at −30°C to rhodomycinone to afford good yields of α-linked antibiotics.[103] Interestingly, the Kolar group applied this same approach using 4-amino and 3,4-diamino analogs of natural sugars for linkage to rhodomycin. In this case, some conditions with TMSOTf catalysis of 1-OpNbz donors gave the desired glycosides and in others, a second glycosyl transfer took place at the hindered tertiary alcohol of the aglycone (Eq. (62)).[104] The Priebe group has reported related results with 1-OTBDMS donors.[105] The Monneret group has reported further developments since the Thiem review. Using the acetates of protected amino sugars where the amine and hydroxyl of daunosamine and acosamine are interchanged (i.e. 4-amino-2,4,6-instead of 3-amino-2,3,6-trideoxy-L-lyxo and arabinopyranoses) activated by *p*-TosH in the presence of daunomycin afforded two new (α-glycosidic) anthracyclines in 20% yield. The experimental report does not reveal the presence or absence of the unnatural β-glycoside anomers.[106] In a study of heterocyclic A-ring analogs of daunomycin, Monneret used Koenigs–Knorr procedures to link deoxyfucosyl chloride to an aglycone with a secondary alcohol with exclusive α-stereochemistry in greater than 90% yield (Eq. (63)). The same coupling to a primary alcohol analog led to an 85:15 α:β mixture. The same primary aglycone was glycosylated with the glycal of daunosamine plus *p*-TosH catalyst to produce a 35% yield of a 75:25 α:β mixture (Eq. (64)). When the acosamine glycal was used in this system, a 26% yield of 1:1 α:β mixture was obtained.[107]



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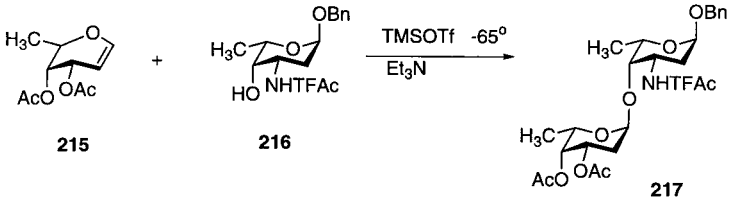

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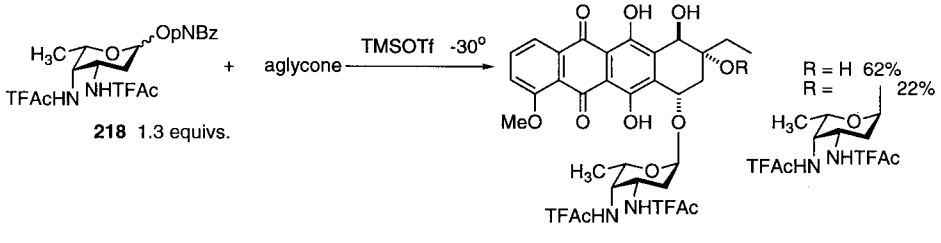

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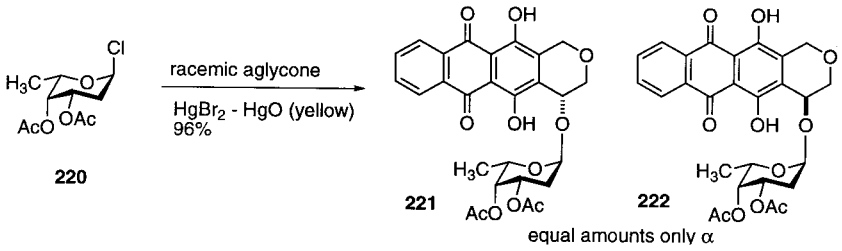

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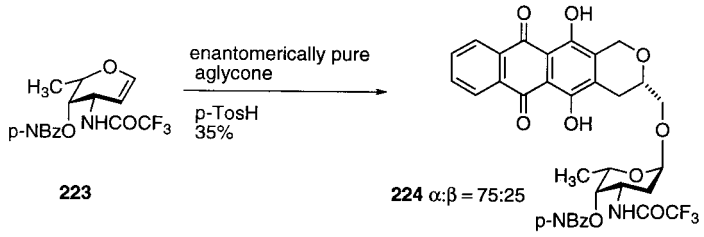
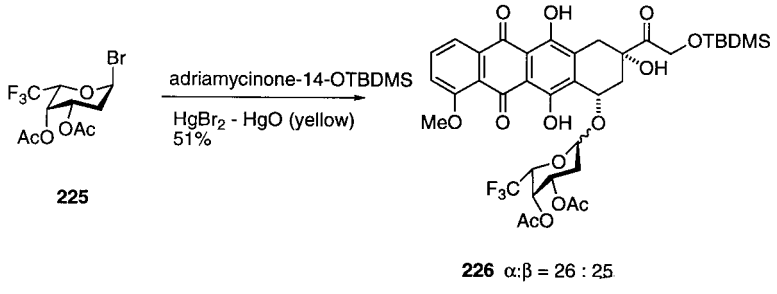


(64)

The natural disaccharide for musettamycin was obtained via Koenigs–Knorr reaction (HgO, $HgBr_2$, mol. sieves) of an unstable bromo-L-fucose donor contaminated with its methyl glycoside precursor and a daunosamine acceptor. The desired α-disaccharide was obtained in 40% yield along with about 45% of 1,1-linked dimer of the donor.[108] For the synthesis of unnatural disaccharide related to that found in musettamycin, the Monneret group used classic Koenigs–Knorr chemistry to link 1-chlorofucose to the 4-OH of a 3-azido 2,3,6-trideoxy-L-glucose material. The disaccharide was obtained in 72% yield as the α-anomer.[109] The natural musettamycin disaccharide was then carried through to the trisaccharides of marcellomycin and aclacinomycin A by using the Thiem methodology, namely the disaccharide acceptor plus NIS plus 3,4-di-*O*-acetyl-L-fucal and 4-*O*-acetyl-L-amicetal respectively. The desired α-iodo trisaccharides were obtained in essentially identical 70% yields. Hydrogenolysis of the iodo functions then afforded the ultimate trisaccharides. Koenigs–Knorr chemistry was also exploited to prepare the trifluoromethyl analog of the 2-deoxy-L-fucosyl derivative of adriamycin. The desired α-L along with the β-L product were formed in equal amounts in 50% overall yield (Eq. (65)). Neither the fluoro sugar or the phenylthio derivative yielded any coupling product of this trifluoromethyl-deactivated sugar.[110] Fluorine substitution at C-14 of the aglycone has no effect on its glycosylation. Thus, 3 different 2-deoxysugar donors were coupled to the fluoro-aglycone in high yield and α-selectivity via TMSOTf activation of an anomeric ester (Eq. (66)).[111] Natural aranciamycinone, an unusual anthracyline, is glycosylated with 2-methoxy-L-rhamnose. The Bols group has described the synthesis of two 2-deoxy analogs via glycosyl transfer of 2-deoxyfucosyl and 2-deoxyglucosyl acetates catalyzed by TMSOTf to produce α-anomers in 37% and 46% yields respectively (Eq. (67)).[112] The 2-deoxyglucosyl product was unstable under the room temperature reaction conditions and could only be isolated when the reaction was carried out at −15°C. Koenigs–Knorr methodology was used to couple daunosamine and 2,6-dideoxyglucosyl derivatives to a hydroxyethyl extended aglycone. The daunosamine coupling afforded a 56:24 α:β mixture while the glucose derivative afforded a 29:25 α:β product.[113] A protected daunosamine glycal was directly coupled by Lednicer to a racemic ring-contracted daunomycin analog with *p*-TosH as catalyst to afford a diastereomeric mixture of a novel analog in 55% yield (Eq. (68)).[114]



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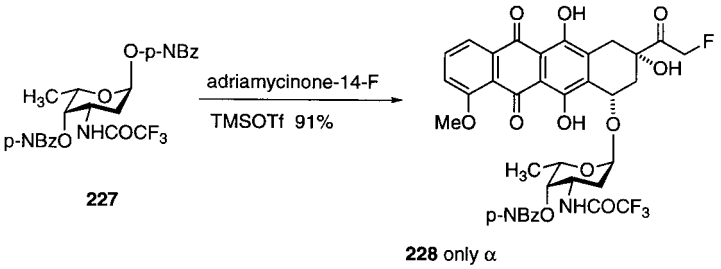

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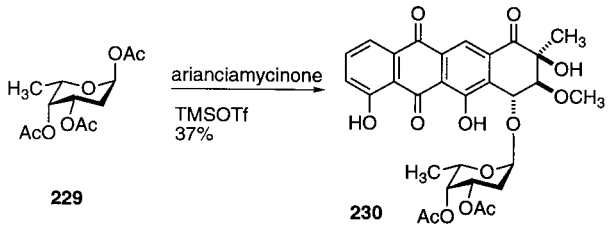

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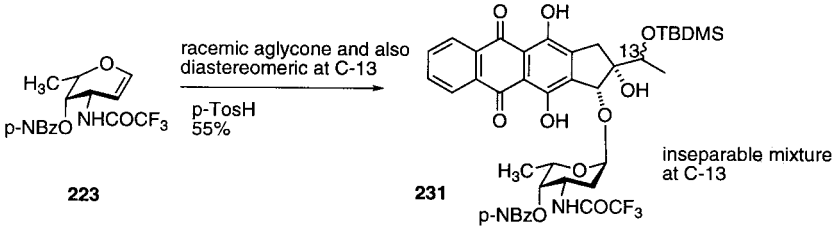
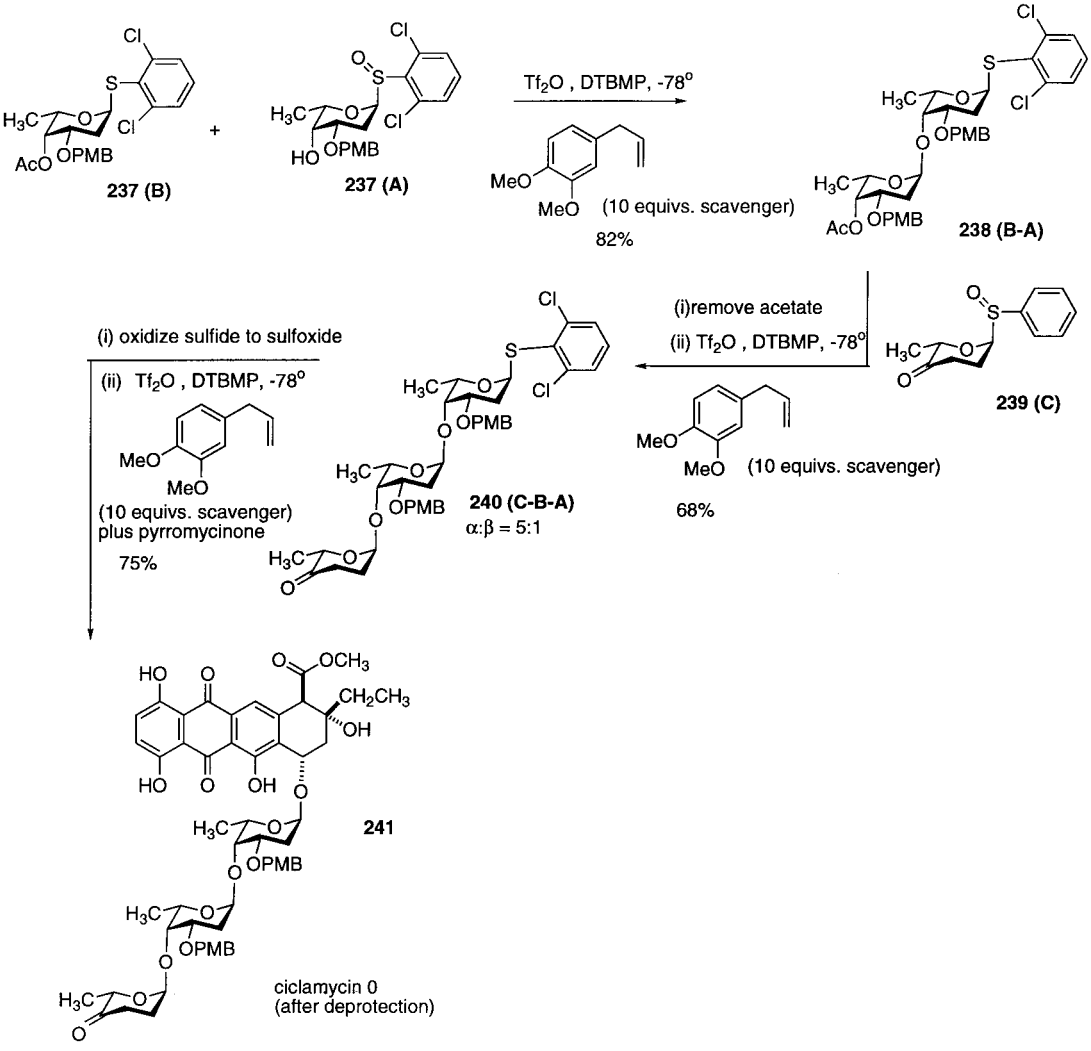


(68)

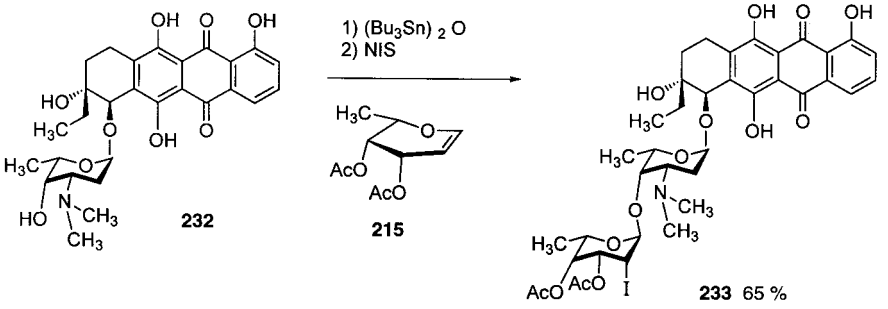
For the synthesis of novel 6-azido-2-deoxypyranoside derivatives of daunomycin, the Koenigs–Knorr method was used with a D and L chloro donor. Interestingly, the D donor afforded an α:β ratio of 1:2 while the enantiomeric donor afforded an α:β ratio of 1.7:1 in unstated yields.[115]

Kahne has applied his sulfoxide activation method to the synthesis ciclamycin 0 (Scheme 4). In his initial report, the one-step synthesis of the required trisaccharide was described. A sequential activation of sulfoxide A (**237**) which glycosylated



Scheme 4.

thioglycoside B (**237**) followed by activation of sulfoxide C (**239**) and its glycosylation of the newly formed A–B disaccharide (**238**) was a notable achievement. In the follow-up full paper, the problem of the one-pot approach, namely the unwanted glycosyl transfer chemistry initiated by the phenylsulfenyl triflate leaving group from sugar sulfoxide A (**237**), was addressed. The newer approach includes a scavenger for the phenylsulfenyl triflate as well as a less-activated sulfide for sugar A (**237**). The modified version results in an 82% yield of A–B α-disaccharide **238**, a 68% yield of the A–B–C trisaccharide **240** as a 5:1 α:β mixture and finally a 75% yield for the coupling of the trisaccharide to the aglycone.[116] The Thiem and Horton groups have used the NIS-glycal activation method to prepare anthracycline derivatives, e.g. in the synthesis of deoxyfucosyl disaccharide units in the anthracyclines[117] (Eq. (69)) and in the glycosylation of a disaccharide glycal with daunomycinone (Eq. (70)). Reduction with Bu_3SnH gave the 2-deoxy-α-glycoside in 55% yield.[118]



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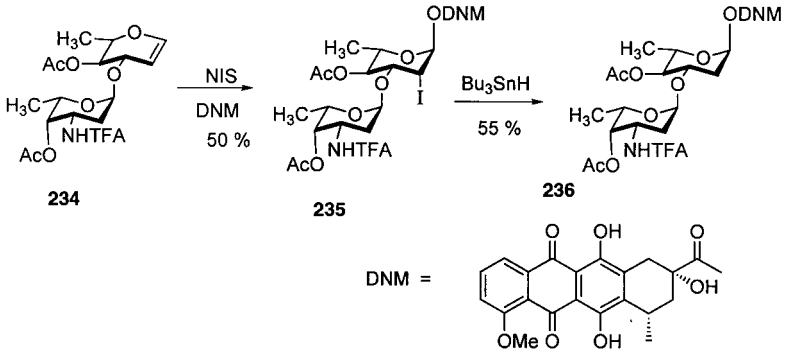
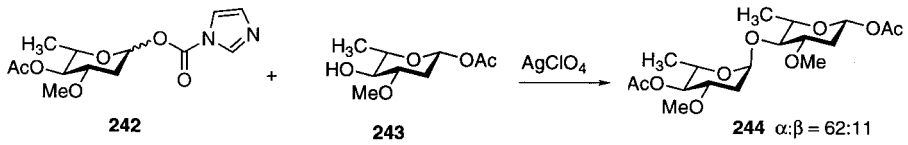


(70)

Avermectin B_{1a} is a macrolide antibiotic glycosylated with an L-oleandrosyl oleandrose disaccharide. Ley has described a total synthesis of the antibiotic which describes the forging of both α-oleandrosyl linkages. He first prepared the disaccharide **244** by activating L-oleandrose-4-acetate as a carbonyl imidazolide and coupling it with oleandrose-1-*O*-acetate using silver perchlorate catalyst. The α-glycoside was obtained in 62% yield along with 11% of the easily separated β-product. This disaccharide diacetate was then selectively deprotected at the anomeric acetate by the use of Superhydride ($LiBEt_3H$) at −78°C. The anomeric OH was activated as its thiocarbonyl imidazolide and the so activated disaccharide **245** was coupled to the aglycone, again with silver perchlorate catalysis, to afford the α-linked product **246** in 64% yield along with 16% of the separable β-anomer (Eq. (71)).[119] Blizzard reported the synthesis of 'spacer'mectin analogs of avermectin with two different disaccharide donors and three different aglycones with short spacer arms. The disaccharide fluoride donor, activated with silver perchlorate and stannous fluoride in ether solvent afforded the α-isomer in 21% yield and the β-isomer in 23% yield for one spacer arm and 14% and 10% for a slightly longer spacer. With thiopyridyl activated disaccharide and another slightly different spacer, silver triflate catalysis afforded 35% α and 24% β products (Eq. (72)).[120] Oleandrose as an α-glycoside, is also found in oleandomycin. The natural antibiotic has been prepared via linkage of oleandrose glycal and camphorsulfonic acid catalysis to the required C-3 OH of the aglycone (Eq. (73)).[121] The desired α-glycoside is reported to be the major product and afforded a 40% yield of the natural product after two deprotection steps. The Danishefsky group also achieved the total synthesis of the related avermectin A_{1a}, an antiparasitic agent, via NIS coupling of an L-glycal derivative with the avermectin A_{1a} aglycon, followed by reductive deiodination with tributyltin hydride and AIBN (Eq. (74)).[122] The selenium electrophile approach has also been used to prepare the disaccharide moiety of Avermectin A_{2b} (Eq. (75)).[75]The avermectin disaccharide was synthesized from the donor 1,4-di-*O*-acetyl-3-*O*-methyl-2-*O*-pivaloyl-a-L-rhamnopyranose and acceptor methyl 3-*O*-methyl-2-*O*-pivaloyl-α-L-rhamnopyranoside using TMSOTf activation. Selective removal of the acetate group and photoirradiation gave directly the tetradeoxydisaccharide (Eq. (76)).[123] The glycal-CSA approach described for oleandromycin synthesis described in Eq. (73) was applied by two groups to the synthesis of the proper glycoside of elaiophylin (azalomycin B) (Eq. (77)). L-Fucal, protected either as TBDMS or IPDMS ethers was coupled via camphorsulfonic acid catalysis to form exclusively an α-glycoside linked to a fragment intended for incorporation onto the macrolide ring.[124] Evans has described an interesting incorporation of D-cymarose onto a fragment destined to become cytovaricin. Cymarose has an axial methoxyl group at carbon 3, i.e. it is a 2,6-dideoxyallose derivative. It is coupled via its anomeric acetate and catalysis with trityl perchlorate. At −20°C, the β:α ratio is 1:3 whereas at −3°C, the ratio turns over to β:α of 4:1, the β-anomer being that required for the natural product

(Eq. (78)). When the TES protecting group was replaced by acetate, the equilibration did not take place and a 1:1 mixture of anomers was obtained.[125]



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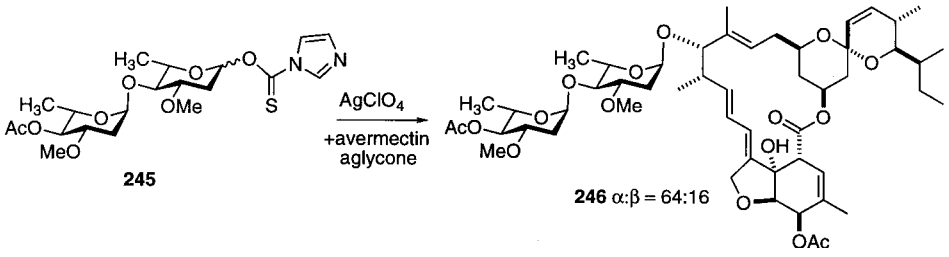

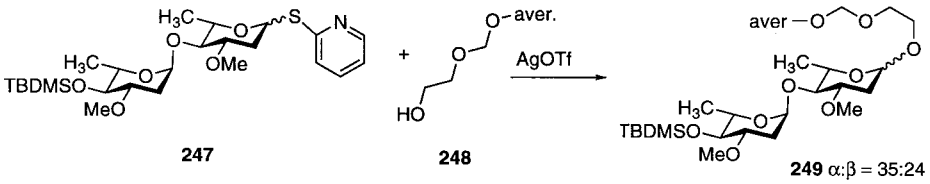

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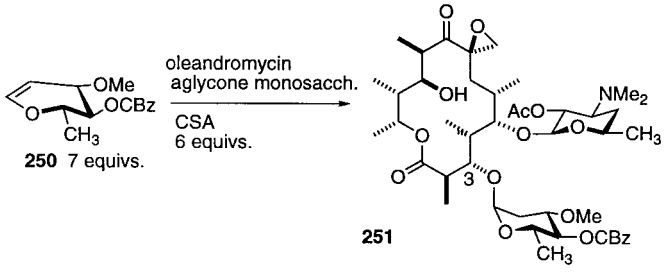

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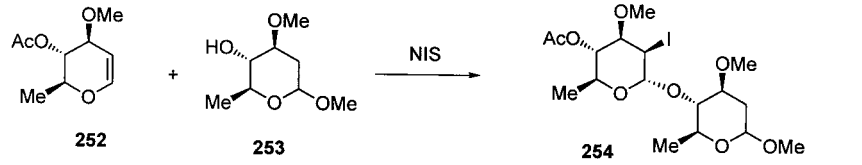

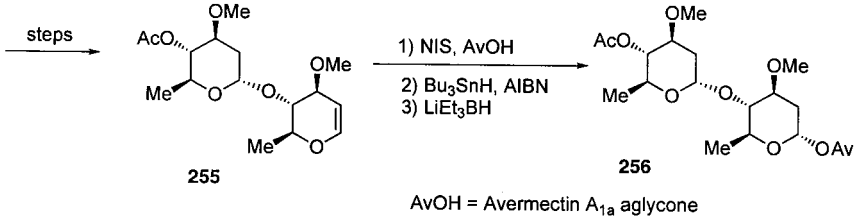

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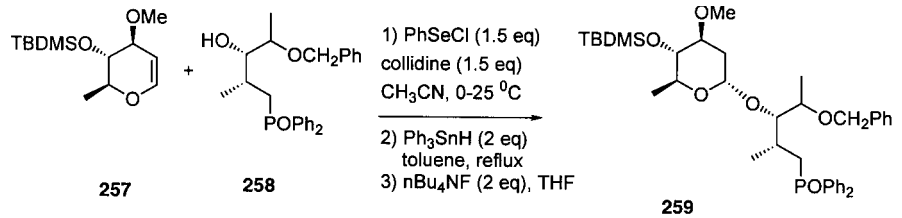

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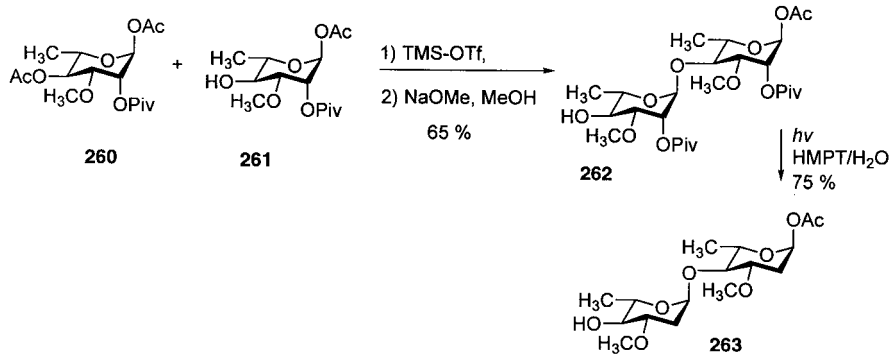
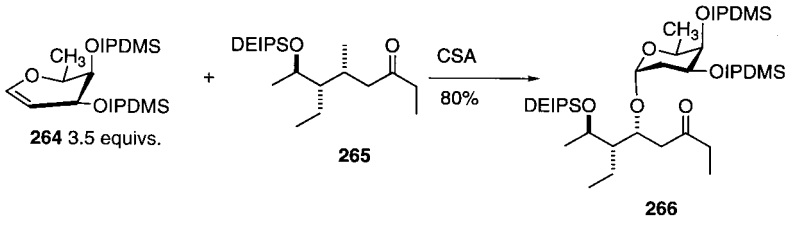
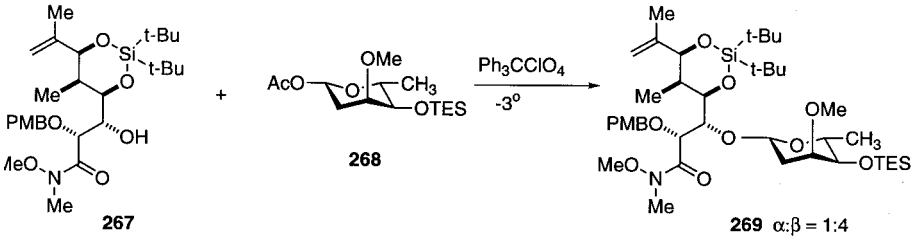


260 261 262 263 (76)

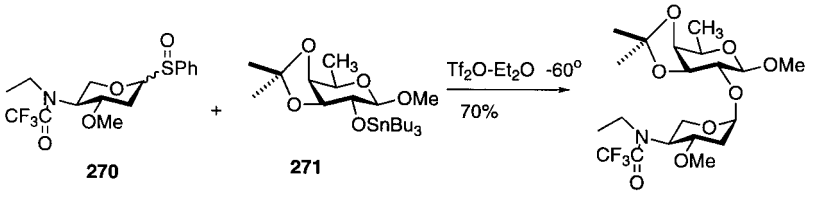


264 3.5 equivs. 265 266 (77)

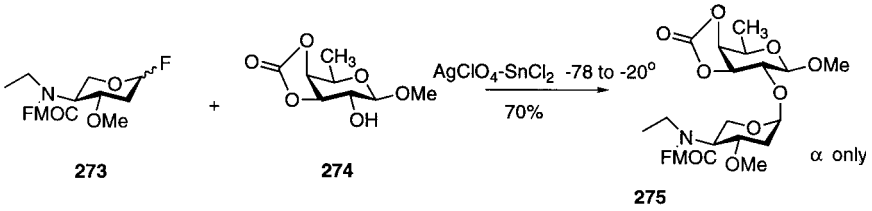


267 268 269 α:β = 1:4 (78)

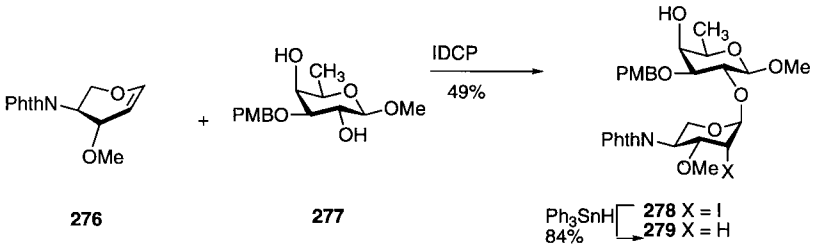
The ene-diyne family of antibiotics incorporate novel 2-deoxyglycoside links. Kahne has described the application of his sulfoxide activation method to the ene-diyne series. Thus, the 2-deoxy sulfoxide of a protected amino sugar, activated by triflic anhydride at −60°C couples to a fucose acceptor via its 2-stannyl ether to yield a disaccharide in 70% yield with better than 12:1 α-selectivity (Eq. (79)). The same method is also used to couple a dideoxyallose sulfoxide donor to both ethoxycarbonyl hydroxylamine and 4-hydroxymethyl-glucosyl acceptors. The selectivities and yields for the key couplings are not reported, just the final yields of the desired and deprotected isomers.[126] The identical ene-diyne disaccharide was prepared by Nicolaou using a glycosyl fluoride donor with $AgClO_4$–$SnCl_2$ catalysis to produce a 4.5:1 α:β anomeric mixture in 70% overall yield (Eq. (80)).[127] Danishefsky prepared the same disaccharide via iodonium (sym collidine) treatment of a glycal in the presence of the fucose acceptor. A 49% yield of iodo disaccharide was obtained which was then deiodinated by triphenyltin hydride in refluxing benzene in 89% yield (Eq. (81)).[128]



270 271 272 α:β = >12:1 (79)



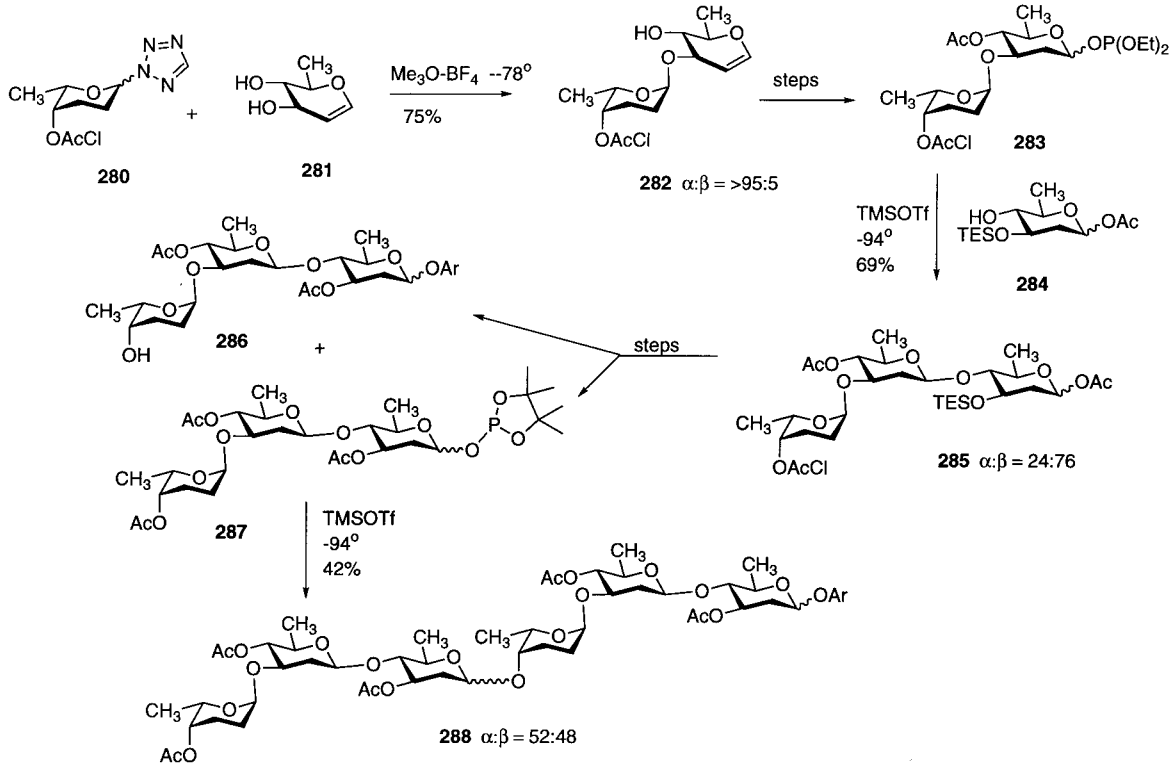
273 274 275 (80)



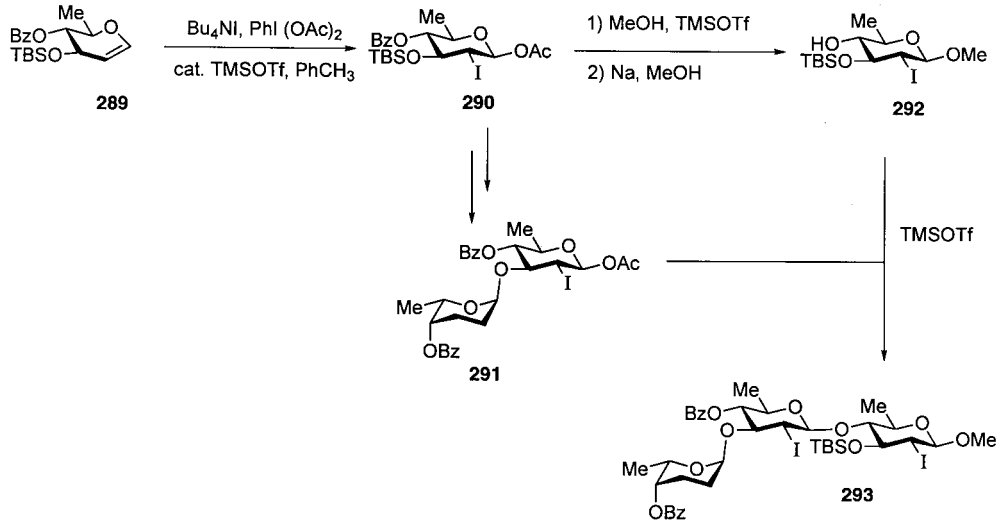
(81)

Landomycin A is an angucycline antibiotic with a hexasaccharide composed of 2,6-dideoxy and 2,3,6-trideoxy sugars linked as β,β,α,β,β,α starting with the aglycone linked to the first sugar. Sulikowski has described an outstanding achievement in the 2-deoxyglycoside field with a synthesis of the hexasaccharide using both tetrazole and phosphite activating groups (Scheme 5). The tetrazole-linked 2,3,6-trideoxy sugar **280**, activated with trimethoxonium fluoborate afforded an α-linked disaccharide in 75% yield. The disaccharide, activated as its diethyl phosphite at −94°C with TMSOTf catalysis produced a key trisaccharide **285** in 69% yield with α:β selectivity of 24:76. The key linkage of two trisaccharide units created via a pinacol phosphite activator with TMSOTF at −94°C produced the hexasaccharide product **288** unselectively (52:48, α:β) in 42% yield.[129] Kirschning used β iodoacetate donors to construct the β glycosidic linkages in the repeating A–B–C trisaccharide in Landomycin A (Scheme 6). Iodoacetoxylation of 4-*O*-benzoyl-3-*O*-tertbutyldimethylsilyl-D-rhamnal gave a 2:1 mixture of β-gluco:α-manno configured iodoacetates from which **290** was isolated by column chromatography. The iodoacetate **290** was then selectively deprotected and coupled to form disaccharide **291** and glycosylated with methanol, then deprotected to afford **292**. TMSOTf assisted glycosylation of **291** and **290** gave trisaccharide **293** in 24% yield. Following the completion of this manuscript, another report on the synthesis of the Landomycin A hexasaccharide appeared.[130] Roush used a similar approach to construct the saccharide chain; the iodoacetate donors were converted to the iodotrichloroacetimidates then coupled using TBSOTf catalysis. A high level of stereocontrol (>95:5) was reported for each of the five glycosidic linkages formed.

The aureolic acid family of antitumor antibiotics include three structurally similar molecules:olivomycin A, mithramycin and chromomycin A_3. The mode of action of these molecules is believed to be due to their ability to bind in GC rich regions of the minor groove of doubly stranded DNA as 2:1 antibiotic/Mg^+ complexes. The Thiem group made pioneering contributions to the synthesis of the di- and trisaccharides of these antibiotics. The work was done in the early and mid-80s before the period encompassed by this review.[131] Binkley has described a detailed study with two 3-axial acyloxy-2-deoxysugar donors, the 1-chloro and 1-ethylthio derivatives (Eq. (82)). Yields were moderate to poor with a variety of different catalysts. In several examples, glycal elimination provided serious competition to glycoside formation.[132] Binkley reported the successful application of the silver silicate modification of the Koenigs–Knorr to prepare a 2-deoxyfucosyl-2,6-dideoxyglucosyl disaccharide in

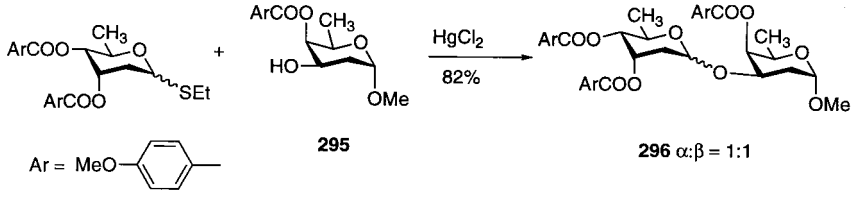


Scheme 5.

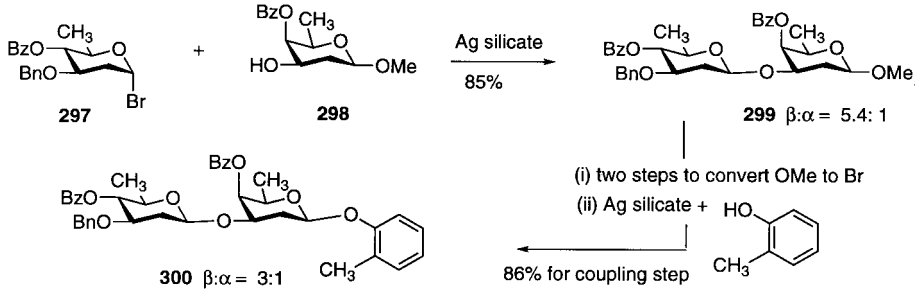


Scheme 6.

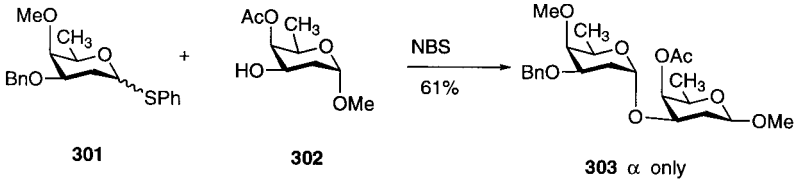
85% yield from the fucosyl bromide donor with a β:α ratio of 5.4:1. The disaccharide was then linked to a model phenolic aglycone using the same method to afford product in 86% overall yield, but with reduced β:α selectivity (3:1) (Eq. (83)).[133] Roush has described a synthesis of the A–B disaccharide of olivomycin which includes a total synthesis of the monosaccharide precursors. The glycoside coupling used the thiophenyl-2-deoxyfucose donor with a 2-deoxyfucose acceptor using NBS as the catalyst at −42°C. The desired product was obtained in yields ranging from 79 to 95% with almost perfect α-selectivity (Eq. (84)).[134] Recently, the first total synthesis of an aureolic acid antibiotic, olivomycin A, was reported by Roush and coworkers (Schemes 7 and 8).[65] Their approach to the synthesis of this molecule involved, first, the coupling of the C sugar residue to the aglycone, followed by the sequential addition of the D–E disaccharide, then the A–B disaccharide. Glycal **304** served as a precursor for both the C and D sugars.[80,70] The A and B sugars was prepared from glycal **305a** and the precursor for the E sugar was glycal **306**.[135] Glycal **305a** was protected to give glycal **305b**. Addition of PhSeCl, then reaction with AgOAc afforded the diequatorially substituted 2-selenophenyl fucosyl acetate **307**. Desilylation of **304**, then iodoglycosylation with protected glycal **305b** gave the α-linked A–B disaccharide **308**. The C-sugar was then coupled to the aglycone **312**. Activation of the glycal **304** by addition of PhSCl, hydrolysis of the anomeric chloride and preparation of the α-anomeric



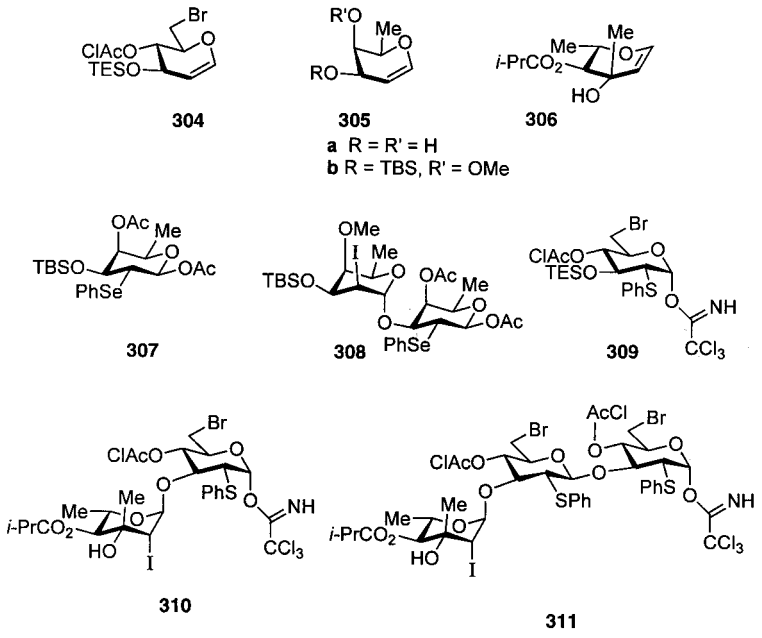
(82)



(83)

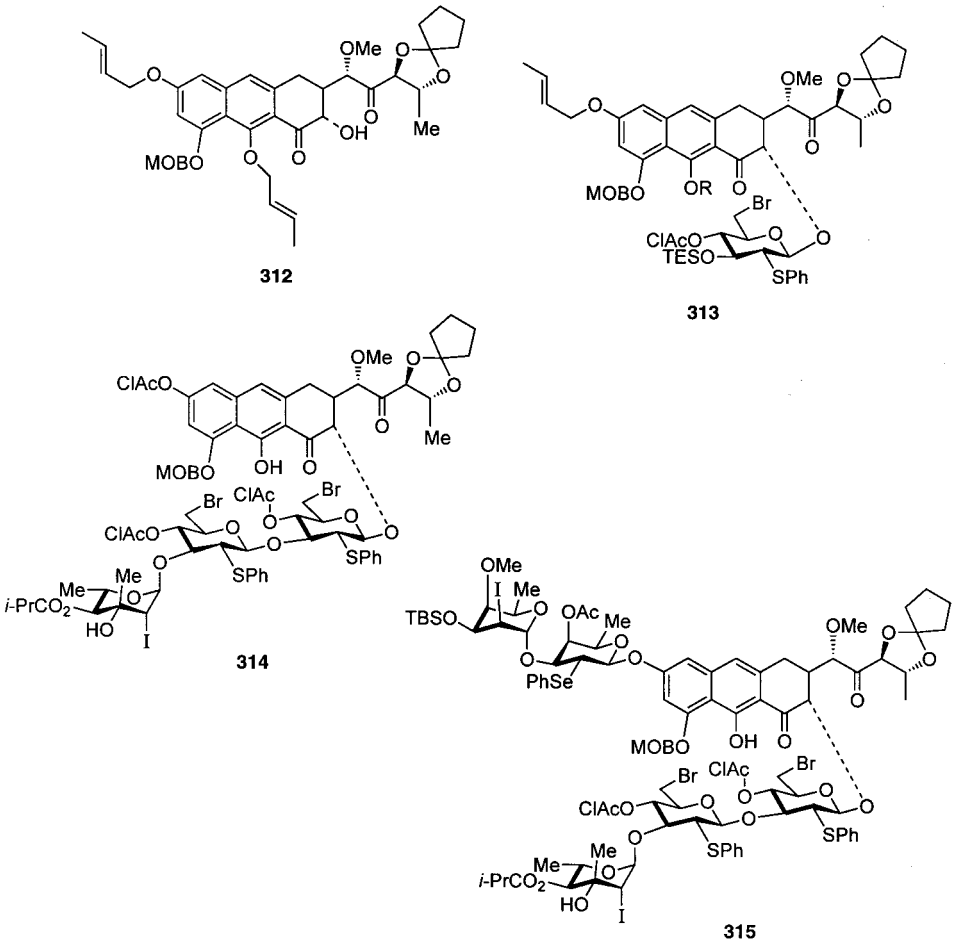


(84)



Scheme 7.

trichloroacetimidate afforded protected C sugar donor **309**. This donor was coupled with the aglycone using TBSOTf as a catalyst to afford **313** in 51% yield. Treatment of glycal **306** with NIS and HOAc afforded olivomycose iodoacetate. The α-linked D–E fragment was then prepared by first desilylating the glycal **304** then reacting it with the olivomyacose iodoacetate using TMSOTf catalysis (74% yield). The E–D glycal was then converted to the E–D trichloroacetimidate **309** by: reaction



Scheme 8.

with PhSCl, hydrolysis and trichloroacetimidate formation. The E–D trichloroacetimidate **309** when coupled with the aglycone-C sugar fragment (3 equiv. of imidate, 0.3 equiv. of TBSOTf) afforded the aglycone–C–D–E fragment **314** in 78% yield. After removal of the phenolic trichloroacetate group, intermediate **314** was coupled with A–B disaccharide under Mitsunobu conditions[122] (73–79% yield). Deprotection of the sugars and aglycone, then reductive removal of the halogen and selenophenyl substituents with Bu_3SnH and triethylborane, and the thiophenyl and BOM substituents with Ra Ni, afforded a totally synthetic (−) olivomycin A **315** with spectral and chromatographic properties identical to authentic samples.

3. Conclusions

In this review we have attempted to compile the relevant literature since 1988 describing the synthesis of 2-deoxyglycosides. These reported methods were grouped according to the type of control element at the C-2 position of the sugar donor. We have also described the applications of these methods to the synthesis of natural products containing 2-deoxysugars. Where possible, direct comparisons were made between the different methods on the issues of scope, yields, selectivities, ease of preparation of the donor sugar and the ease of conversion of the glycoside to the 2-deoxyglycoside.

It is left to the readers of this review to draw their own conclusions on the choice of sugar donors to be utilized in synthetic transformations leading to 2-deoxyglycosides. Of the various methods presented, some are very easy to use; i.e. the donor requires very few preparative steps and/or the conversion to the 2-deoxysaccharide is trivial. In these cases, the selectivities for the desired product may not be high and chromatographic separation of isomers is necessary. An excess of donor or acceptor is usually used in the glycosylation reaction. For example, the Falck–Mioskowski method gives useful α-selectivity for glucal and galactal directly for a variety of acceptors (Eq. (29)). An excess of acceptor is employed (sometimes up to four fold) and chromatography is normally needed. Another facile and selective, yet not as universal method for the preparation of α-glycosides, is the NIS (IDCP) protocol (Eqs (35)–(38). Here, a second reductive step must be implemented to form the 2-deoxysaccharide.

The separation of a mixture of diastereomers from a glycosylation reaction using contemporary chromatographic techniques is usually a routine procedure. Because of this, the choice of a direct glycosylation reaction is often more desirable. In fact, sometimes it may even be advantageous to synthesize both diastereoisomers of a natural product for biological evaluation. In other instances, only low yields of the product are obtained in the direct approach. Sometimes using excesses of an acceptor in a glycosylation reaction is not expedient; i.e. if the acceptor requires multiple steps to prepare or is the degradation product of a precious, naturally occurring compound. By the careful choice and placement of directing groups in a preformed glycosyl donor it can sometimes be possible to obtain good yields of a single diastereoisomer from a coupling reaction. The preformed glycosyl donors frequently permit the use of near stoichiometric quantities of both acceptor and donor. Often the coupling reactions work even in the presence of acceptors of low reactivity in the direct glycosylation protocols. The less valuable donor is synthesized in several steps from readily available precursors. The construction of the saccharide chains of the antibiotics landomycin A (Scheme 6) and olivomycin A (Schemes 7 and 8) were carried out using this strategy. The iodoacetate and iodotrichloroacetimidate donors were prepared from glycals. Glycosylations of the iodoacetate and iodoimidate donors with alcohols and TMSOTf gave excellent β-selectivities and good yields of saccharides without requiring large excesses of acceptor. A second reductive step was required to obtain the 2-deoxysaccharides. Likewise, the Sulikowski glycosyl tetrazoles and phosphites gave good selectivities for α- and β-2-deoxyglycosides, respectively, with only slight excesses of alcohol acceptors (Scheme 5). These donors were prepared from 2-deoxypyranose sugars and glycals.

In the last decade, a great deal of work has been done developing methods for the synthesis of 2-deoxyglycosides; important structural components of many natural products. Much progress has been made. Ultimately, the distinction between these methods is one of simplicity versus selectivity.

Note Added in Proof

We omitted the following from Section 2.2: McDonald has used the *N*-iodosuccinimide activation of glycals to form a glycoside using a chiral alkynol acceptor. This alkynolated glycoside after de-iodination, is itself then cyclized to a disaccharide glycal using a tungsten catalyst. This entire process can be iterated to make trisaccharide materials.[136] Also omitted from Section 2.6 was a discussion of cycloadditions by our group and the Capozzi group where glycosides are formed by a novel heterocycloaddition related to that illustrated in Eq. (48). The cycloadducts formed are then directly desulfurized to form steroidal[137] and aryl 2-deoxyglycosides.[138]

References

1. (a) Barresi, F.; Hindsgaul, O. *Chemically Synthesized Oligosaccharides*; 1994; A Searchable Table of Glycosidic Linkages, *J. Carbohydr. Chem.* **1995,** *14*, 1043–1087. (b) Barresi, F.; Hindsgaul, O. Glycosylation Methods in Oligosaccharide Synthesis. In *Modern Synthetic Methods*; 1995; pp 281–330.
2. Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285–333.

3. Kirschning, A.; Bechtold, A. F. W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 2–84.
4. Hallis, T. M.; Liu, H. *Acc. Chem. Res.* **1999**, *32*, 579–588.
5. Hashimoto, S-I.; Sano, A.; Sakamoto, H.; Nakajima, Y.; Yanagiya, Y.; Ikegami, S. *Synlett* **1995**, 1271–1273.
6. Paterson, I.; McLeod, M. D. *Tetrahedron Lett.* **1995**, *36*, 9065–9068.
7. Muller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 4763–4766.
8. Li, H.; Chan, M.; Zhao, K. *Tetrahedron Lett.* **1997**, *38*, 6143–6144.
9. Koch, A.; Lamberth, C.; Wetterich, F.; Giese, B. *J. Org. Chem.* **1993**, *58*, 1083–1089.
10. Bielawska, H.; Michalska, M. *J. Carbohydr. Chem.* **1991**, *10*, 107–112.
11. Laupichler, L.; Sajus, H.; Thiem, J. *Synthesis* **1992**, 1133–1136.
12. Yamanoi, T.; Inazu, T. *Chem. Lett.* **1990**, 849–852.
13. Sun, L.; Li, P.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 7147–7150.
14. Toshima, K.; Nozaki, Y.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 6887–6890.
15. Ge, M.; Thompson, C.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 11014–11015.
16. Brown, D. S.; Ley, S. V.; Vile, S.; Thompson, M. *Tetrahedron* **1991**, *47*, 1329–1342.
17. Jutten, P.; Scharf, H-D.; Raabe, G. *J. Org. Chem.* **1991**, *56*, 7144–7149.
18. Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1874–1876.
19. Noecker, L.; Duarte, F.; Giuliano, R. M. *J. Carbohydr. Chem.* **1998**, *17*, 49–59.
20. Takeuchi, K.; Higuchi, S.; Mukaiyama, T. *Chem. Lett.* **1997**, 969–970.
21. The use of other dehydrating agents have been shown to promote direct dimerization of pyranose and furanose sugars into 1,1′-disaccharides: Posner, G. H.; Bull, D. S. *Tetrahedron Lett.* **1996**, *37*, 6279–6282
22. Toshima, K.; Nagai, H.; Matsumura, S. *Synlett* **1999**, 1420–1422.
23. Petrakova, E.; Glaudemans, C. P. J. *Glycoconjugate J.* **1994**, *11*, 17–22.
24. Finizia, G. *J. Carbohydr. Chem.* **1998**, *17*, 75–98.
25. Fillion, G.; Dupraz, B.; Prudhomme, N.; Huynh-Dinh, T. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1485–1490.
26. (a) Crich, D.; Ritchie, T. J. *Chem. Commun.* **1988** 1461–1463. (b) Crich, D.; Ritchie, T. *J. Carbohydr. Res.* **1989**, *190*, c3–c6. (c) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Perkin Trans. I* **1990**, 945–954. (d) Crich, D.; Hermann, F. *Tetrahedron Lett.* **1993**, *34*, 3385–3388.
27. Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716–8717.
28. Mereyala, H. B.; Kulkarni, V. R.; Ravi, D.; Sharma, G. V. M.; Rao, B. V.; Reddy, G. B. *Tetrahedron* **1992**, *48*, 545–562.
29. Ravi, D.; Kulkarni, V. R.; Mereyala, H. B. *Tetrahedron Lett.* **1989**, *30*, 4287–4290.
30. Furukawa, H.; Koide, K.; Takao, K-i.; Kobayashi, K. *Chem. Pharm. Bull.* **1998**, *46*, 1244–1247.
31. (a) Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *Chem. Commun.* **1990**, 270–272. (b) Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R. *Chem. Commun.* **1988**, 823–825. (c) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am.Chem. Soc.* **1988**, *110*, 5583–558.
32. Takahashi, Y.; Vasella, A. *Helvet. Chim Acta* **1992**, *75*, 1563–1571.
33. Inanaga, J.; Yokoyama, Y. *Hanamoto Chem Lett.* **1993**, 85–88.
34. Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *J. Am. Chem. Soc.* **1991**, *113*, 6982–6992.
35. Matsumoto, T.; Hosoya, T.; Suzuki, K. *Tetrahedron Lett.* **1990**, *31*, 4629–4632.
36. Hayman, C. M.; Larsen, D. S.; Brooker, S. *Aust. J. Chem.* **1998**, *51*, 545–553.
37. Junneman, J.; Lundt, I.; Thiem, J. *Liebigs Ann Chem.* **1991**, 759–764.
38. Toshima, K.; Misawa, M.; Ohta, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1989**, *30*, 6417–6420.
39. Schene, H.; Waldmann, H. *Chem. Commun.* **1998**, 2759–2760.
40. Nicolaou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rubsam, F.; Rodriguez, R. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1872–1874.
41. Motoki, K.; Morita, M.; Kobayashi, E.; Uchida, T.; Akimoto, K.; Fukushima, H.; Koezuka, Y. *Biol. Pharmcol. Bull.* **1995**, *18*, 1487–1491.
42. Zhang, Z.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 2383–2393.
43. Bolitt, V.; Mioskowski, C.; Lee, S-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812–5813.
44. Kaila, N.; Blumenstein, M.; Bielawska, H.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 4576–4578.
45. Andrews, F. L.; Larsen, D. S. *Tetrahedron Lett.* **1994**, *35*, 8693–8696.
46. Kaila, N.; Yu, H-A.; Xiang, Y. *Tetrahedron Lett.* **1995**, *36*, 5503–5506.
47. Nicolaou, K. C.; Trujillo, J. L.; Chibale, K. *Tetrahedron* **1997**, *53*, 8751–8778.
48. Paulsen, H.; Rutz, V.; Brockhausen, I. *Liebigs Ann Chem.* **1992**, 735–745.
49. Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468–5472.
50. (a) Flekhter, O. B.; Baltina, L. A.; Tolstikov, G. A. *Russ. Chem. Bull.* **1997**, *46*, 1335–1338. (b) Flekhter, O. B.; Baltina, L. A.; Spirikhin, L. V.; Baikhova, I. P.; Tolstikov, G. A. *Russ. Chem. Bull.* **1998**, *47*, 513–516.
51. Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937–4940.
52. Mereyala, H. B.; Ravi, D. *Tetrahedron Lett.* **1991**, *32*, 7317–7320.
53. Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 3471–3475.
54. Mouton, C.; Tillequin, F.; Seguin, E.; Monneret, C. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2055–2060.
55. Booma, C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1995**, *36*, 5807–5810.
56. Toshima, K.; Nagai, H.; Ushiki, Y.; Matsumara, S. *Synlett* **1998**, 1007–1009.
57. Wieczorek, E.; Thiem, J. *Synlett* **1998**, 467–468.
58. Oscarson, S.; Tedebark, U. *Carbohydr. Res.* **1995**, *278*, 271–287.
59. (a) Thiem, J.; Kopper, S. *Tetrahedron* **1990**, *46*, 113–138. (b) Kopper, S.; Thiem, J. *Carbohydr. Res.* **1994**, *260*, 219–232.

60. Baltina, L. A.; Flekhter, O. B.; Vasil'eva, E. V.; Tolstikov, G. A. *Russ. Chem. Bull.* **1995**, *44*, 1979–1980.
61. Baltina, L. A.; Flekhter, O. B.; Vasil'eva, E. V.; Tolstikov, G. A. *Russ. Chem. Bull.* **1997**, *46*, 582–584.
62. (a) Paulsen, H.; Springer, M.; Reck, F.; Meinjohanns, E.; Brockhausen, I.; Schachter, H. *Liebigs Ann.* **1995**, 53–56. (b) Paulsen, H.; Springer, M.; Reck, F.; Brockhausen, I.; Schachter, H. *Carbohydr. Res.* **1995**, *275*, 403–411.
63. Friesen, R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656–6660.
64. Izumi, M.; Ichikawa, Y. *Tetrahedron Lett.* **1998**, *39*, 2079–2082.
65. Kopper, S.; Springer, D.; Thiem, J. *J. Carbohydr. Chem.* **1994**, *13*, 1065–1070.
66. Roush, W. R.; Briner, K.; Sebesta, D. P. *Synlett* **1993**, 264–266.
67. Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990–1991.
68. (a) Roush, W. R.; Narayan, S.; Bennett, C. E.; Briner, K. *Org. Lett.* **1999**, *1*, 895–897. (b) Roush, W. R.; Narayan, S. *Org. Lett.* **1999**, *1*, 899–902.
69. Lafont, D.; Boullanger, P.; Rosenzweig, M. *J. Carbohydr. Chem.* **1998**, *17*, 1377–1393.
70. Kirschning, A.; Eur *J. Org. Chem.* **1998**, 2267–2274.
71. Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891–893.
72. Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541–3542.
73. (a) Thiem, J.; Schottmer, B. *Agnew. Chem., Int. Ed. Engl.* **1987**, *26*, 555–557. (b) Sajus, H.; Thiem, J. *Liebigs Ann. Chem.* **1993**, 211–213.
74. Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723–2726.
75. (a) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084–2092. (b) Franck, R. W.; Kaila, N. *Carbohydr. Res.* **1993**, *239*, 71–83. (c) Ramesh, S.; Franck, R. W. *Chem. Commun.* **1989**, 960–961.
76. Hashimoto, S.; Yanagiya, Y.; Honda, T.; Ikegami, S. *Chem. Lett.* **1992**, 1511–1514.
77. Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837–8852.
78. Toshima, K.; Mukaiyama, S.; Nozaki, Y.; Inokuchi, H.; Nakata, M.; Tatsuta, K. *J. Am. Chem. Soc.* **1994**, *116*, 9042–9051.
79. (a) Toshima, K.; Nozaki, Y.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1993**, 5761–5764. (b) Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1995**, *117*, 3717–3727.
80. Capozzi, G.; Dios, A.; Franck, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Agnew. Chem., Int. Ed. Engl.* **1996**, *35*, 777–779.
81. Dios, A.; Nativi, C.; Capozzi, G.; Franck, R. W. *Eur. J. Org. Chem.* **1999**, 1869–1874.
82. (a) Marzabadi, C. H.; Franck, R. W. *Chem. Commun.* **1996**, 2651–2652. (b) Franck, R. W.; Marzabadi, C. H. *J. Org. Chem.* **1998**, *63*, 2197–2208.
83. Capozzi, G.; Mannocci, F.; Menichetti, S.; Nativi, C.; Paoletti, S. *Chem. Commun.* **1997**, 2291–2292.
84. Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 6501–6514.
85. Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L.; van Delft, F. L. *Agnew. Chem., Int. Ed. Engl.* **1998**, *37*, 1874–1876.
86. Barrett, A. G. M.; Miller, T. *Tetrahedron Lett.* **1988**, *29*, 1873–1874.
87. Perez, M.; Beau, J. *Tetrahedron Lett.* **1989**, *30*, 75–78.
88. Sebesta, D. P.; Roush, W. R. *J. Org. Chem.* **1992**, *57*, 4799–4802.
89. Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, 1947–1948.
90. Gurjar, M. K.; Ghosh, P. K. *Indian J. Chem.* **1988**, 1063–1064.
91. (a) Trumtel, M.; Veyrieres, A.; Sinay, P. *Tetrahedron Lett.* **1989**, *30*, 2529–2532. (b) Trumtel, M.; Tavecchia, P.; Veyrieres, A.; Sinay, P. *Carbohydr. Res.* **1989**, 29–51.
92. Marino-Albernas, J. R.; Bittman, R.; Peters, A.; Mayhew, E. *J. Med. Chem.* **1996**, *39*, 3241–3247.
93. Castro-Palomino, J. C.; Schmidt, R. R. *Synlett* **1998**, 501–503.
94. Scharf, H.; Zagar, C. *Carbohydr. Res.* **1993**, *248*, 107–118.
95. (a) Danishefsky, S. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Gervay, J.; Danishefsky, S. *J. Org. Chem.* **1991**, *56*, 5448–5451.
96. Hirschmann, R. et al., *J. Am. Chem. Soc.* **1993**, *115*, 12550–12568.
97. Sato, K.; Yoshimoto, A. *Chem. Lett.* **1995**, 39–40; Sato, K.; Yoshimoto, A.; Takai, Y. *Bull. Chem. Soc. Jpn* **1997**, *70*, 885–890.
98. Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5796–5798.
99. Gaudenzi, L.; Apparao, S.; Schmidt, R. R. *Tetrahedron* **1990**, *46*, 277–290.
100. Coleman, R. S.; Fraser, J. R. *J. Org. Chem.* **1993**, *58*, 385–392.
101. (a) Arcamone, F.; Animati, F.; Berettoni, M.; Bigioni, M.; Capranico, G.; Casazza, A. M.; Caserini, C.; Cipollone, A.; Franciotti, M.; Lombardi, P.; Madami, A.; Manzini, S.; Monteagudo, E.; Polizzi, D.; Pratesi, G.; Righetti, S. C.; Salvatore, C.; Supino, R.; Zunino, F. *J. Nat. Can. Inst.* **1997**, *89*, 1217–1223. (b) Animati, F.; Arcamone, F.; Berettoni, M.; Cipollone, A.; De Cesare, M.; Franciotti, M.; Lombardi, P. *J. Chem. Soc., Perkin Trans. I* **1996**, 1327–1329.
102. (a) Kolar, C.; Kneissl, G.; Wolf, H.; Kampchen, T. *Carbohydr. Res.* **1990**, *208,* 111–116. (b) Kolar, C.; Kneissl, G. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 809–811.
103. Kolar, C.; Dehmel, K.; Moldenhauer, H.; Gerken, M. *J. Carbohydr. Chem.* **1990**, *9*, 873–890.
104. Kolar, C.; Dehmel, K.; Moldenhauer, H. *Carbohydr. Res.* **1990**, *208*, 67–81.
105. Priebe, W.; Grynkiewicz, G.; Neamati, N. *Tetrahedron Lett.* **1991**, *32*, 2079–2082.
106. Martin, A.; Monneret, C.; Pais, M. *Carbohydr. Res.* **1987**, *166*, 59–70.
107. Dufat-Trinh Van, H.; Seguin, E.; Tillequin, F.; Monneret, C.; Koch, M. *Chem. Pharm. Bull.* **1989**, *37*, 3294–3300.
108. Monneret, C.; Martin, A.; Pais, M. *J. Carbohydr. Chem.* **1988**, *7*, 417–434.
109. Ramiliarison, C.; Monneret, C. *J. Carbohydr. Chem.* **1989**, *8*, 723–734.

110. Takagi, Y.; Nakai, K.; Tsuchiya, T.; Takeuchi, T. *J. Med. Chem.* **1996**, *39*, 1582–1588.
111. Matsumoto, T.; Ohsaki, M.; Yamada, K.; Matsuda, F.; Terashima, S. *Chem. Pharm. Bull.* **1988**, *36*, 3793–3804.
112. Bols, M.; Binderup, L.; Hansen, J.; Rasmussen, P. *Carbohydr. Res.* **1992**, *235*, 141–149.
113. Jizba, J.; Sedmera, P.; Prikrylova, V.; Vokoun, J.; Mikulik, K.; Vanek, Z. *Coll. Czech. Chem. Commun.* **1989**, *54*, 1104–1117.
114. Tu, C-y. J.; Lednicer, D. *J. Org. Chem.* **1987**, *52*, 5624–5627.
115. Menyhart, M.; Kover, K.; Sztaricskai, F. *J. Carbohydr. Chem.* **1990**, *9*, 253–267.
116. (a) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580–1581. (b) Gildersleeve, J.; Smith, A.; Sakurai, K., Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 6176–6182.
117. Thiem, J.; Klaffke, W. *J. Org. Chem.* **1989**, *91*, 2006–2009.
118. Horton, D.; Priebe, W.; Sznaidman, M. L.; Varela, O. *J. Antibiot.* **1993**, 1720–1730.
119. Ley, S. V.; Armstrong, A.; Diez-Martin, D.; Ford, M. J.; Grice, P.; Knight, J. G.; Kolb, H. C.; Madin, A.; Marby, C. A.; Mukherjee, S.; Shaw, A. N.; Slawin, A. M. Z.; Vile, S.; White, A. D.; Williams, D. J.; Woods, M. *J. Chem. Soc. Perkin Trans. 1* **1991**, 667–692.
120. Blizzard, T.; Margiatto, G.; Linn, B.; Mrozik, H.; Fisher, M. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 369–372.
121. Tatsuta, K.; Kobayashi, Y.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975–3978.
122. Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109*, 8119–8120.
123. Rainer, H.; Scharf, H.; Runsink, J. *Liebigs. Ann. Chem.* **1992**, 103–107.
124. (a) Wakamatsu, T.; Nakamura, H.; Naka, E. *Tetrahedron Lett.* **1986**, *27*, 3895–3898. (b) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn* **1988**, *61*, 2369–2381.
125. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.
126. (a) Yang, D.; Kim, S.-H.; Kahne, D. *J. Am. Chem. Soc.* **1991**, *113*, 4715–4716. (b) Walker, S.; Gange, D.; Gupta, V.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 3197–3206.
127. Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.; Smith, A. L.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7593–7611.
128. Halcomb, R. L.; Wittman, M. D.; Olson, S. H.; Danishefsky, S. J.; Golik, J.; Wong, H.; Vyas, D. *J. Am. Chem. Soc.* **1991**, *113*, 5080–5082.
129. Guo, Y.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 1392–1397.
130. Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124–6125.
131. Thiem, J.; Gerken, M.; Schottmer, B.; Weigand, J. *Carbohydr. Res.* **1987**, *164*, 327–341.
132. Binkley, R. W.; Koholic, D. J. *J. Carbohydr. Chem.* **1988**, *7*, 487–499.
133. (a) Binkley, R. W.*J. Carbohydr. Chem.* **1990** *9*, 507–511. (b) Binkley, R. W.; Sivik, M. R.*J. Carbohydr. Chem.* **1991** *10*, 399–416. (c) Binkley, R. W.; Koholic, D. J. *J. Org. Chem.* **1989**, *54*, 3577–3581.
134. (a) Roush, W. R.; Lin, X.; Straub, J. A. *J. Org. Chem.* **1991**, *56*, 1649–1655. (b) Roush, W. R.; Straub, J. A. *Tetrahedron Lett.* **1986**, *27*, 3349–3452.
135. Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236–2250.
136. McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246–4247.
137. Win, W. W.; Franck, R. W. *J. Org. Chem.* **1997**, *62*, 4510–4512.
138. Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Rafaelli, B. *Chem. Eur. J.* **1999**, *5*, 1748–1754.

Biographical Sketch

Cecilia H. Marzabadi received her A.B. and M.S.(R) degrees in Chemistry from St. Louis University, where she performed research with Professor Harold Dieck. After a brief period of industrial employment, she continued her studies towards her Ph.D. in Chemistry at the University of Missouri-St. Louis. Under the direction of Professor Christopher Spilling, she received her Doctoral degree in Chemistry in the Fall of 1994. Shortly thereafter, she became a Postdoctoral Research Associate in the laboratory of Professor Richard Franck at Hunter College/CUNY. In the fall of 1999, she joined the faculty of the Department of Chemistry and Biochemistry at Seton Hall University as an Assistant Professor. She is the recipient of a Clare Boothe Luce Professorship. Her research interests include synthetic carbohydrate chemistry and natural product synthesis.

Richard W. Franck was born in Germany and emigrated to the U.S. at the age of two. He was educated in the public schools of Springfield MA, received his A.B. at Amherst College in 1958 and earned his Ph.D. working on steroidal alkaloids in the labs of William S. Johnson both at Wisconsin and Stanford. After a short postdoc. (1962-63) with Herbert House at M.I.T., Franck began his academic career at Fordham University in 1963. His group made early contributions in the mitomycin synthesis field, including the first assembly of its tetracyclic framework. His introduction to carbohydrate chemistry began around 1980 with work on the synthesis of olivomycin. Also at about that time, Franck moved his group about 10 miles south to Hunter College where he is Distinguished Professor. Early work on the cycloadditions of carbohydrate glycals evolved into the 90's with the discovery, with his colleague and co-inventor Prof. Giuseppe Capozzi of Florence, of a cycloaddition method for the synthesis of 2-deoxyglycosides. Most recently, the Franck group has been developing the Ramberg–Backlund reaction as a general method for *C*-glycoside synthesis.