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Preparation and reactions of iodo sugars

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1. Introduction

Iodine-containing sugars serve as useful intermediates in synthetic carbohydrate chemistry; as stereodirecting groups in glycosylation reactions and glycal addition reactions, as good leaving groups useful in the formation of carbohydrate derived heterocycles, and as readily removable functionalities for the preparation of deoxy sugars. This review will examine advances in the preparation and utilization of iodine-containing sugars in the last decade (2000–2009).[1,2] Glycosyl iodide donors, iodoglycosylation chemistry of glycals, the preparation of iodine-containing glycals and their further transformations and the preparation of carbohydrate-based

Abbreviations: AcOH, acetic acid; Ac_2O, acetic anhydride; Arg, arginine; Asp, asparagine; 9-BBN, 9-borabicyclo[3.3.1]nonane; *n*-BuOH, *n*-butanol; TBS, *tert*-butyldimethylsilyl; *t*-BuLi, *tert*-butyllithium; TMS, trimethylsilyl; DBU, 1,8-diazabicycloundec-7-ene; DCM, dichloromethane; DIB, (diacetoxyiodo)benzene; DMF, *N*, *N*-dimethylformamide; Et_2O, diethyl ether; Fmoc, fluorenylmethyloxycarbonyl; Gly, glycine; KDO_D, 3-deoxy-D-*manno*-2-octulosonic acid; KHMDS, potassium bis(trimethylsily)amide; LPS, lipopolysaccharide; MeCN, acetonitrile; MeOH, methanol; NIS, *N*-iodosuccinimide; OTf, trilate; SLeX, Sialyl Lewis X; Tf_2O, triflic anhydride; TfOH, triflic acid; THF, tetrahydrofuran; TMSI, trimethylsilyl iodide; TTBP, tris(tribromoneopentyl)phosphate; TTMSS, tris(trimethylsilane).

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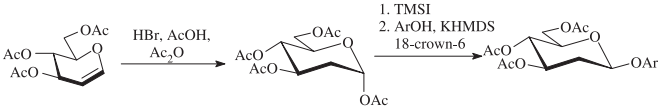
heterocycles via iodine-containing sugars will be discussed in detail. We will not attempt to extensively cover the preparation and reactions of carbohydrates containing iodine at the C-3, C-4, and C-6 positions as there are far too many examples in the recent literature. Instead, we will highlight new methodology for the installation and use of these substituted sugars. Topics not covered in this review include the preparation of nucleosides containing iodine in the heterocycle and the use of iodine as a catalyst in the transformations of carbohydrates.

2. Preparation of C-1 and C-2 iodo sugars

2.1. Glycosyl iodides

In recent years, several groups have reinvestigated the usefulness of glycosyl iodides as glycosyl donors. This methodology originally came to prominence in the 1980s and was more or less abandoned because of the presumed difficulty associated with the preparation of these donors or because of their presumed instability.[3] Several newer methods have been reported for the preparation of glycosyl iodides and these donors have been reported to be useful for the synthesis of both α- and β- glycosides.

Glycosyl iodides were reported to be readily synthesized from the corresponding anomeric acetates by treatment with trimethylsilyl iodide (TMS-I). Thus, treatment of pyranose sugars with TMS-I, followed by reaction with tetra-*n*-butylammonium cyanide or tetra-*n*-butylammonium azide afforded β-cyano- and β-azidosugars in good yields.[4] Likewise, glycals when reacted with HBr, followed by TMS-I, afforded the 2-deoxy-glycosyl iodides in good yields (Scheme 1). Treatment of the intermediate α-glycosyl iodides with aryl alkoxy anions provided selectively 2-deoxy-β-*O*-aryl glycosides, presumably via a direct displacement reaction.[5]



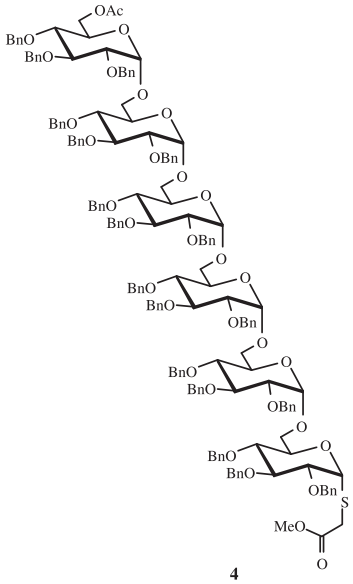
1 2 3

Scheme 1. Preparation of β-aryl glycosides via glycosyl iodide donors.

Alpha-linked disaccharides could also be obtained by the addition of tetra-*n*-butylammonium iodide to a solution of α-iodide donor, alcohol acceptor and base.[6] This *in situ* anomerization strategy was used to construct a mannose–mannose disaccharide, in route to a high mannose construct.

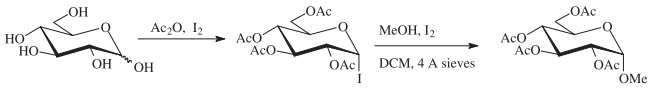
Glycosyl iodide donors have also been used in both solid- and solution-phase syntheses yielding α-(1→6)-linked glucose oligomers in near quantitative yields.[7] The solid-phase strategy offered advantages in terms of ease of purification, however, this method required 7.5 equiv of donor and approximately 12 h to complete glycosylation. In contrast, solution-phase methods required only 2.5 equiv of donor and 2–3 h reaction time per glycosylation. The overall advantages of solution-phase oligosaccharide synthesis were further illustrated in the convergent synthesis of a hexamer (methoxycarbonylmethyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-tetrakis-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6))-2,3,4-tri-*O*-benzyl-1-thio-D-glucopyranoside) **4** that was constructed from dimer donor iodides in a two-plus-two and a two-plus-four fashion (Fig. 1).

Whereas these previously mentioned papers focused mainly on the use of 'armed' pyranosyl iodides or on the *in situ* anomerization of iodide donors in glycosylation strategies, Field, et al. investigated the use of fully acetylated pyranosyl iodides ('disarmed' donors) in glycoside synthesis.[8] These donors were prepared in two steps from unprotected pyranose sugars by the addition of acetic anhydride and iodine, followed by treatment with hexamethyldisilazane (HMDS) and additional iodine (Scheme 2).[9]



4

Figure 1. α-Gluco hexasaccharide **4** synthesized by solution-phase glycosylation.



5 6 7

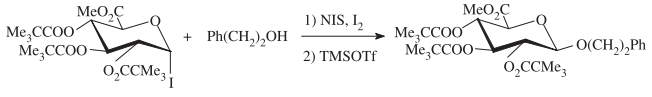
Scheme 2. Peracetylated glycosyl iodide donors.

Glycosylation reactions with the fully acetylated glycosyl iodides gave mixed results, depending on the alcohol acceptor employed.[9] For example, with methanol, exclusively the α-glycosidic product **7** was obtained. However, when other alcohol acceptors were used, the proportion of β-glycoside increased; for 6-bromohexanol, a 65% yield of anomers (1.7:1, α/β) was obtained. A change in sugar protecting groups from acetates to benzoates also led to exclusive β-glycoside formation in modest yields.

Glycosyl iodides of protected 2-amino-2-deoxy-D-glucose were also prepared *in situ* with TMS-I and were reacted with a variety of *O*-, *N*-, *S*- and *C*-nucleophiles to form the corresponding β-glycosides in good yields.[10]

Stachulski et al. reported in a series of papers [11–13] on the preparation and use of a 'disarmed' glucuronyl iodide donor **8**. The highly selective reaction of methyl tetra-*O*-pivaloyl-β-D-glucopyranuronate with iodotrimethylsilane or $(Me_3Si)_2$ and I_2 afforded, in excellent yield, the 'disarmed' glycosyl iodide, which had good stability at 20 °C and excellent stability at 0 °C. An X-ray crystal structure of **8** was obtained.[11]

Glycosylation reactions of the glucuronyl donor were carried out with a variety of aglycones. When a series of primary and secondary alcohols was reacted with the donor using *N*-iodosuccinimide (NIS) followed by trimethylsilyl triflate (TMSOTf), yields of 60–83% of β-glucuronides were obtained (Scheme 3).[12]



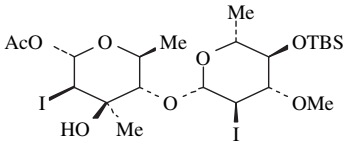
8 9 10

Scheme 3. Glycosylation with glucuronyl iodide donors.

Alpha-glucuronyl iodide **8** is also an efficient donor for the β-glucuronidation of a range of steroidal secondary alcohols. Ketone and ester functional groups in the steroid were tolerated and yields of 60–70% were obtained without using large excesses of the donor.[13]

2.2. 2-Iodo-glycosyl donors

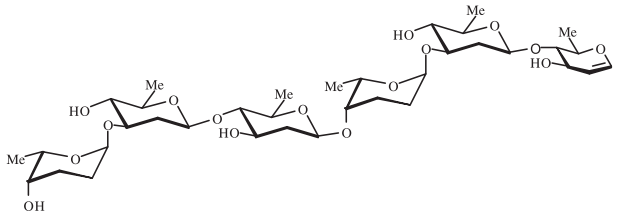
2-Deoxy-2-iodoglycosylacetates continued to be used successfully in the synthesis of 2-deoxy-β-glycosides. Roush reported the successful synthesis of the disaccharide unit of Apoptolidin A **11** via the regio- and stereoselective TBS-OTf-promoted β-glycosidation reaction of 2,6-dideoxy-2-iodo-β-glucopyranosyl acetate and *p*-methoxybenzyl 2,6-dideoxy-2-iodo-3-*C*-methyl-α-mannopyranoside. The disaccharide was obtained in 87% yield (α/β 40:60).[14]



11

Because of the occurrence of 2,6-dideoxy-β-galactoside units in many of the aureolic acid antibiotics, including mithramycin and UCH9, as well as in the durhamycins, Roush investigated the use of 2-deoxy-2-iodo-galactosyl acetates and trichloracetimidates to fashion this linkage.[15] The best selectivity for the β-glycosidic linkage was achieved by using 6-deoxy-3,4-carbonate-protected galactosyl donors. Glycosylation selectivity in these reactions was believed to be dictated by the conformational preference of the intermediate oxocarbenium ion. With non-bridging protecting groups at C-3 and C-4, conformational flexibility was predicted to be present in the donor and mixtures of glycosides were obtained when activated with tributylsilyl triflate (TBSOTf). When the 3- and 4-positions of the galactose ring were tied up with a cyclic carbonate, this group observed yields greater than 60% and >8:1 β/α selectivity.

The highly stereoselective synthesis of hexasaccharide glycal **12** (Fig. 2), a precursor to the Landomycin A hexasaccharide, was achieved using 2-deoxy-2-iodo-glucopyranosyl trichloroacetimidate donors. Each of the three 2-deoxy-β-glycosidic linkages in **12** was established with 95% selectivity using this technology.[16]

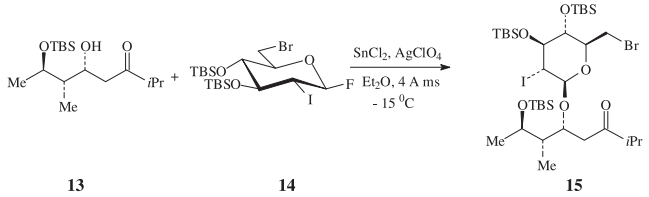


12

Figure 2. Glycal precursor to the Landomycin hexasaccharide.

Roush et al. also investigated the mechanism of this high β-selectivity of glycosylation reactions of 2-iodo-trichloroacetimidate donors. The use of sterically-constrained 4,6-*O*-benzylidene glycosyl imidates gave some insight into the likely pathway of these glycosidation reactions. Using these conformationally constrained donors, it was found that the glycosidations were still highly β-selective. An S_N2-like displacement pathway was discounted because the stereoselectivity of glycosidation was independent of the starting donor configuration. Possible sources of the excellent β-steroselectivity in these reactions with unconstrained donors were proposed to be inverted oxonium ions and in the constrained donors a twist boat conformation and iodonium ion intermediates.[17]

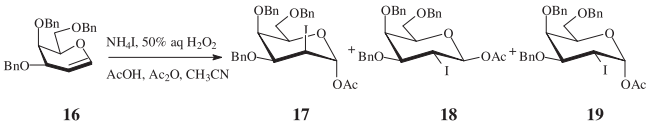
Glycosyl fluorides were also prepared from the 2-deoxy-2-iodoglycosyl acetates by: (1) hydrazinolysis of the anomeric acetate; and (2) treatment with diethylaminosulfur trifluoride (DAST). These 2-iodo fluoride donors **14** proved to be more stable and could be activated under mild conditions. Application of this new glycosyl donor to the glycosidation reactions of a variety of acceptors, including β-hydroxy ketones, afforded β-glycosides **15** with high efficiency and stereoselectivity (65%, β/α >98:2) (Scheme 4). Removal of the C-2 iodo and the C-6 bromo with nBu$_3$SnH and Et$_3$B gave the 2,6-dideoxy sugar (70–90% yield).[18]



13 **14** **15**

Scheme 4. Glycosylation of β-hydroxy ketones with 2-deoxy-2-iodoglycosyl fluorides.

In 2004, Gammon et al. reported an alternative synthesis of 2-deoxy-2-iodoglycosylacetates from glycals. Protected glycals were converted in less than 2 h at low temperatures to 2-deoxy-2-iodoglycosylacetates in high yields and selectivities using the simple, inexpensive reagent mixture of ammonium iodide, hydrogen peroxide and acetic anhydride/acetic acid in acetonitrile. Only the 1,2-*trans* addition products were detected in reactions of protected glycals (glucal and galactal), and in accordance with previous findings, the α-*manno* products predominated except in the case of the per-O-silylated derivatives (β-*gluco*/α-*manno*, 83:17). Some of the *cis* α-*gluco* configured product was obtained in the case of tri-*O*-benzyl-D-galactal (**17**:**18**:**19**, 15:1:4) (Scheme 5). The yields of donors ranged from 82% to near quantitative.[19]



16 **17** **18** **19**

Scheme 5. Mixture of iodoacetate sugars formed from tri-*O*-benzyl-D-galactal.

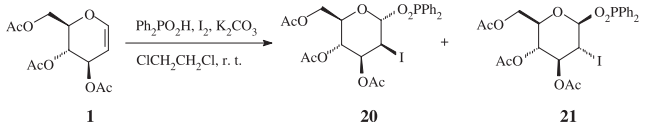
In a subsequent paper, the same group also showed that 1,2-cyclopropanated sugars could be converted to novel 2-deoxy-2-iodomethyl glycosyl acetates using the same combination of reagents.[20]

Iodoacetoxylation chemistry was also employed by Lafont and Boullanger[21] in the synthesis of L-glucosamine glycosyl donors from 3,4,6-tri-*O*-acetyl-L-glucal. Treatment of the glucal with I_2 and $Cu(OAc)_2$ in acetic acid at 80 °C afforded a mixture of *trans*-2-iodoaceteoxy sugars in 79% yield of which the diaxial isomer was preferred (~8:1). Subsequent reaction of the major isomer with $TMSN_3$ and TMSOTf, gave the anomeric azide with retention of configuration at C-1 and C-2. The glycosyl azide was subsequently used as a glycosyl donor.

Iodoacetoxylation reactions have also been conducted on a polymer support using hypervalent iodine reagents. The reaction of glycals with polymer-bound bis(acetoxy)iodate (I) complexes affords 2-iodoglycosyl acetates in good yield. These compounds could be further converted to the 2-deoxy-2-iodoglycosides by treatment with a polymer-bound silyl triflate. The conversion of glycals to glycosides could also be carried out in a 'one pot' sequence in high yields.[22]

In an effort to make mimics of naturally-occurring sugar phosphates, Togo, et al. [23] conducted iodophosphoryloxation reactions of glycal double bonds. Treatment of glycals with a combination of diphenylphosphinic acid and iodine in dichloroethane at room temperature afforded a mixture of trans isomers of which the alpha-*manno* product was predominant (Scheme 6). For tri-*O*-acetyl D-glucal **1**, a 93% yield was obtained (71:22, α-*manno* **20**/β-*gluco* **21**).

The resulting 2-iododiphenylphosphinates could then be converted in high yields to the 2-deoxy derivatives via treatment with triethylborane.

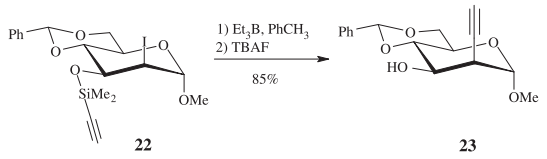


Scheme 6. Iodophosphoryloxation of tri-*O*-acetyl-D-glucal.

2.3. Other transformations of 2-iodo sugars

2-Iodo sugars have also been prepared via the nucleophilic displacement of C-2 triflates with tetra-*n*-*butyl*-ammoniumtriflate. This protocol was employed by Fairbanks, et al. in the cost effective preparation of 4,6-benzylidene-D-glucal from α-methylglucopyranoside.[24] Reductive elimination of the C-2 iodide with zinc dust in acetic acid with a catalytic amount of platonic chloride afforded the desired glucal in 69% yield.

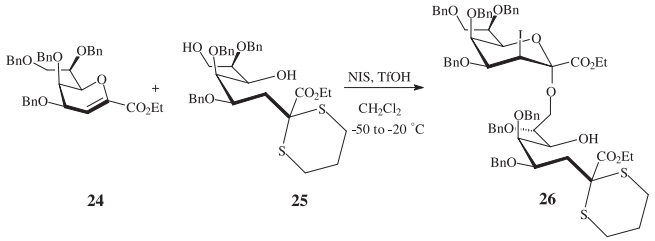
The presence of a C-2 iodo group and free C-3 hydroxy group has been used as a means to introduce and ethynyl group at the C-2 position of the sugar using free radical conditions. Thus, reaction of the C-3 alcohol group of methyl-2-deoxy-2-iodo-4,6-*O*-benzylidene-α-D-mannopyranoside with ethynyl dimethylsilyl chloride and triethylamine produced the C-3 silyl ether **22**. Further treatment with triethylborane, then tetra-*n*-butyl ammoniumfluoride (TBAF) afforded the C-2 ethynyl sugar **23**, presumably by a 5-*exo* cyclization and atom transfer, followed by an elimination (Scheme 7).[25]



Scheme 7. C-2 alkynyl sugar preparation.

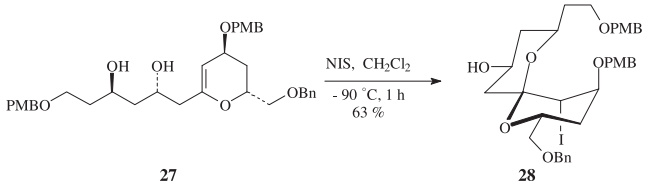
2.4. Iodoglycosylation reactions

The iodoglycosylation chemistry developed by Thiem[26] still figures prominently in synthetic carbohydrate chemistry. In the past decade, there have been several reports of the use of this methodology in the literature. For example, Takahashi used this chemistry to prepare 3-deoxy-D-*manno*-2-octulosonic acid (KDO) derivatives; a component of lipopolysaccharide (LPS) found in the outer membrane of Gram negative bacteria.[27] Thus, treatment of glycal **24** with 1.5 equiv of acceptor **25** in the presence of NIS and triflic acid afforded excellent yields (89%) of the disaccharide **26** (Scheme 8). The acceptor portion of the resulting molecule could be readily converted to a glycal and the glycosylation process could be repeated in an iterative fashion. Removal of the C-3 iodides and cleavage of all the benzyl ether protecting groups could be accomplished using $Pd(OH)_2$/MeOH/*n*-BuOH/ethyl acetate. An acetylation/deacetylation sequence provided tri- and di-α(2,8)-KDO-containing oligosaccharides in good yields.



Scheme 8. Synthesis of KDO derivatives.

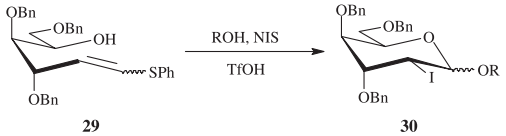
An intramolecular iodospiroketalization reaction was utilized to synthesize the C-D spiroketal unit of Spongistatin 1(Altohyrtin A). This stereoselective cyclization was accomplished by the preferred kinetic, *trans*-diaxial addition to the glycal (8:1 dr) (Scheme 9).[28]



Scheme 9. Iodospiroketalization reaction used in synthesis of Spongistatin 1.

Jung utilized an iodoalkoxylation protocol to install a dimethyl vinyl carbinol group at the anomeric center of different glycals. Subsequent oxidation of the vinyl group to an aldehyde, followed by generation of the C-2 radical from the 2-iodoaldehyde, intramolecular addition of the C-2 radical to the formyl group and β-scission, led to equatorially-disposed C-2 formyl sugars in modest yields.[29]

2-Deoxy-2-iodopyranosides have also been synthesized from 2-deoxy-2-iodoglycosides derived from *E*-sulfanyl alkenes using a 'one pot' consecutive cyclization–glycosylation process (Scheme 10).[30] This procedure has been applied to both the synthesis of steroidal glycosides and to disaccharides. Reductive deiodination at C-2 with tin hydride afforded the 2-deoxyglycosides in good yields.[31] The major products formed were those from 6-*endo* cyclization, in which the iodine at C-2 was in a cis relationship with the alkoxy at C-3. The glycosidic bond in the major isomers was always *trans* to the iodine at C-2.



Scheme 10. Cyclization-glycosylation reactions of *E*-sulfanyl alkenes.

The reactivity of glucosyl and galactosyl donors in a variety of glycosylation conditions was also compared. This included the competitive reaction of octanol and NIS with glycals for the two sugars. The 2-deoxysugar from galactal was formed preferentially (1.4:1) over that from glucal. A more positive transition state was proposed for the galactose sugar, which is more spread out in space with the galactal donor iodonium ion.[32]

2.5. Addition of iodine and nitrogen to glycals

The Danishefsky group reported the successful synthesis of two naturally occurring glycopeptides utilizing, in part, the iodosulfonamidation chemistry developed in this group's lab. A high mannose core containing glycopeptide carrying full H-Type-2 blood group specificity was prepared, spectroscopically characterized and its activity was confirmed using an enzyme linked immunosorbant assay (ELISA).[33] The fucosylated biantennary *N*-glycan of erythropoietin was also synthesized, in part, using this technique.[34]

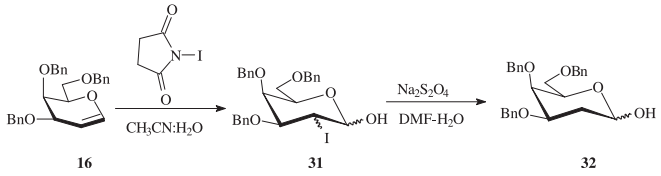
Alkyl, aryl, and heteroaryl glycosylamides were prepared by De Castro and Marzabadi by the addition of the corresponding primary amide and NIS to a series of protected glycals. Treatment with tin hydride afforded the 2-deoxyglycosyl amides in modest yields.[35]

1-Azido-2-iodo *trans*-configured sugars were also prepared from glycals using iodine-based reagents. The two methods that were reported to effect this transformation were: (1) NIS and NaN_3 in

acetonitrile; and (2) a combination of Oxone, KI, NaN_3, and alumina in acetonitrile. These methods were used to prepare methyl *N*-acetyl-α-D-livdosaminide from 4,6-di-*O*-acetyl-3-deoxy D-glucal.[36]

2.6. Iodohydrin formation

Glycals were converted into the corresponding 2-deoxypyranose sugars in good yields by treatment with *N*-iodosuccinimide in CH_3CN–H_2O (95:5) followed by removal of the iodide group using $Na_2S_2O_4$ in DMF:H_2O at room temperature (Scheme 11). This method was mild enough to allow the survival of acid-sensitive groups such as silyl and trityl ethers.[37]



16 31 32

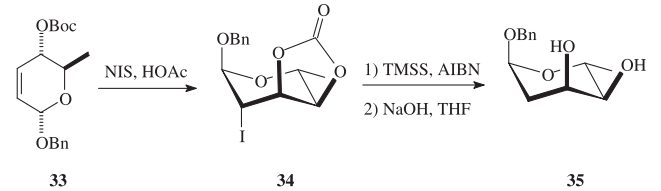
Scheme 11. Preparation of 2-deoxypyranose sugars by the reduction of iodohydrins.

The oxidative iodination of glycals to iodohydrins and iodoethers was also reported using iodide salts and H_2O_2 with tungstate anions exchanged on synthetic takovite-like mineral as a catalyst.[38]

Iodohydroxylation of glycals was also studied using hypervalent iodine reagents. Treatment of tri-*O*-acetyl-D-glucal with I_2 and $PhI(OCOCF_3)_2$ in an acetonitrile/water solvent system afforded a 78% yield of the α-*manno* configured iodohydrin.[39] This methodology was also applied to a variety of other types of alkenes.

Recently, Priebe et al. reported the preparation of iodohydrins and other halohydrins as potential metabolic inhibitors. The electrophilic addition reaction of NIS and water with 3,4,6-tri-*O*-acetyl-D-glucal **1**in toluene at reflux afforded a mixture of *cis*- and *trans*-iodohydrins (*gluco*/*manno*, 2:3 ratio). Silylation of the crude mixture with *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane afforded as the main products the 1-O-silylated β- anomers, with *manno*- and *gluco*- configurations, accompanied by only a minor product having the α-*manno*- configuration. Subsequent chromatography led to a separation of pure isomers in high yield (96.5% total).[40]

Iodohydrins have also been utilized in the synthesis of unusual deoxy sugars. For example, a regioisomeric halohydrin was used to prepare the 2-deoxypyranoside, R-digitoxose **35** from a pyran (Scheme 12).[41] Thus, simply exposing the Boc-carbonate protected pyran **31** to 2.5 equiv of NIS in acetic acid provided an excellent yield of iodocarbonate **34** (96%). The iodine in the iodocarbonate **34** was then reduced by *tris*(trimethylsilyl)silane (TTMSS) under radical conditions in 45% yield. Finally, the cyclic carbonate was hydrolyzed with NaOH in aqueous THF to afford the desired R-digitoxose **35** in 84% yield.



33 34 35

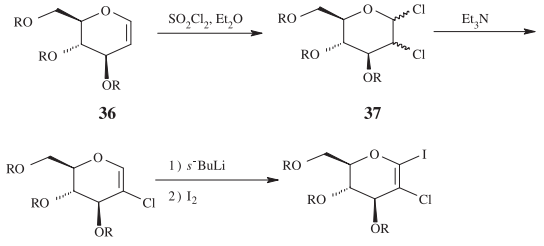
Scheme 12. Preparation of α-digitoxose.

Treatment of 2-deoxy-2-iodopyranoses under dehydrative glycosylation conditions (Ph_2SO, Tf_2O, TTBP) gave mixtures of pyranose glycals, 2-iodoglycals, and 1,1′-disaccharides. While the product distribution revealed that this reaction was very sensitive to the configuration of the 2-deoxy-2-iodopyranose, 2-iodopyranoid glycals could be obtained almost exclusively in good yields by employing a 3,4-*O*-isopropylidene as a cyclic bifunctional protecting group.[42]

3. Iodo sugars with unsaturation

3.1. 1-Iodoglycals

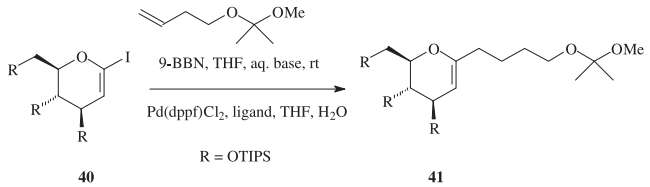
C-1 iodoglycals **39** have been synthesized from 2-deoxy-2-halo-1-lithioglycals (Scheme 13).[43,44]



36 37 38 39

Scheme 13. The preparation of C-1 iodoglycals by lithium–halogen exchange.

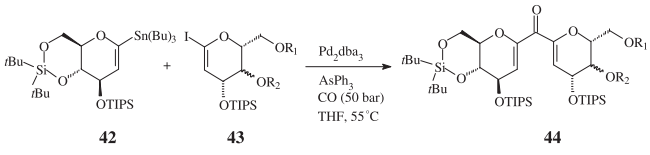
The C-1 iodoglycals have been utilized in a variety of organometallic coupling reactions. Tan, et al.[45] used C-1 iodoglycals to prepare C-1 alkyl and acyl glycosides via Suzuki–Miyaura cross coupling reactions (Scheme 14). This methodology was also utilized by Martin et al. to form the *C*-aryl glycoside as part of a formal synthesis of galtamycinone.[46,47]



40 41

Scheme 14. *C*-glycosides from C-1 iodoglycals via a Suzuki–Miyaura cross coupling.

A Stille coupling reaction was used to prepare C-1-linked disaccharides in both the glucal and galactal series. Yields of coupled products were 81% and 79%, respectively (Scheme 15).[48]



42 43 44

Scheme 15. Stille coupling reaction to prepare C-1, C-1′linked disaccharides.

3.2. 2-Iodoglycals

2-Iodoglycals were prepared from iodohydrins as previously described.[42] These glycals were also utilized in a variety of coupling reactions. Danishefsky, et al. used a Suzuki–Miyaura coupling reaction of a 2-iodoglycal to aid in the construction of the oxadecalin core of the phomaticin A, an antagonist of platelet activating factor (PAF).[49]

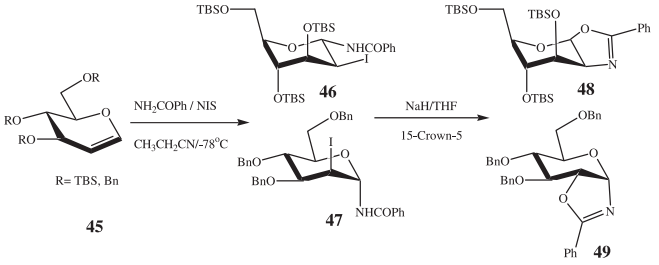
4. Preparation of carbohydrate-containing heterocycles

Carbohydrate-containing heterocycles are widely found in nature. Natural products such as Allosamidin, Trehazolin, and Casuarine-6-O-α-D-glucopyranoside are potent inhibitors of glycosidases. Glycosidases are enzymes involved in the hydrolysis of glycosidic bonds of important polysaccharides found in plants, bacteria, fungi,

and parasites. Because of their biological activity, a great deal of effort has been put forward in order to synthesize analogs of these bioactive natural products bearing the same or similar heterocyclic scaffolds. In this section we will review the use of iodo sugars as precursors in the construction of carbohydrate-based heterocyclic compounds.

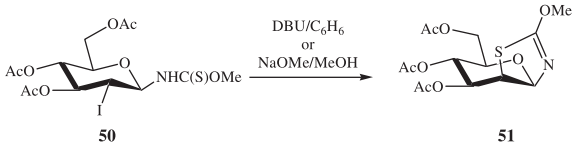
Iodine is a very versatile halogen that can easily undergo nucleophilic displacement. Because of its ease of displacement, iodine has been used in many cyclization reactions involving carbohydrates. Cyclizations involving the internal displacement of iodine from the C-2 position have been widely used in the preparation of carbohydrate fused heterocycles.

In an effort to prepare novel glycooxazolines and glycoaziridines as potential glycosidase inhibitors, Marzabadi and De Castro were able to prepare C-1, *N*- and *O*-glycooxazolines, using 2-deoxy-2-iodoglycosylamides as precursors (Scheme 16).[50] The 2-deoxy-2-iodo sugars were obtained via the addition of NIS to the double bond of various glycals in the presence of aryl and alkyl amides. Treatment of the iodoamides with NaH led to displacement of the iodine at the C-2 position and formation of the oxazoline.



Scheme 16. Preparation of *N*- and *O*-glycooxazolines from 2-deoxy-2-iodo sugars.

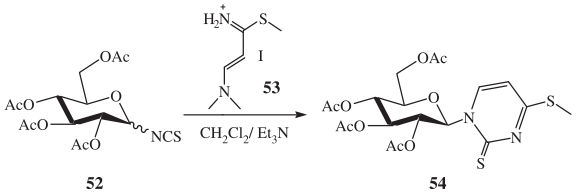
Surprisingly, in some cases, mixtures of two products were isolated from the cyclizations, which were later confirmed by NMR studies to be the *N*- and *O*-glycooxazolines. In the case of the *N*-glycooxazoline adduct, ring formation was achieved upon deprotonation of the amide followed by O-alkylation. The *O*-glycooxazolines were proposed to be formed by migration of the nitrogen from C-1 to C-2 through the formation of the unstable *N*-acylaziridine, which then underwent ring opening and O-alkylation. Factors such as the solvent, the choice of base and the protecting groups on the sugar were reported to have a great influence in the stereoselectivity and the yields obtained in these reactions.



Scheme 17. Preparation of thiazoles from 2-deoxy-2-iodosugars.

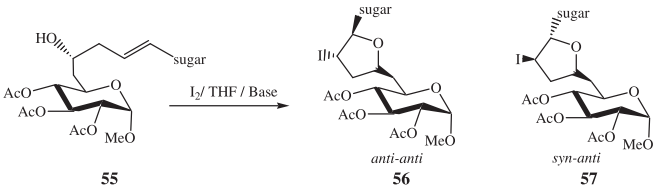
Similar carbohydrate fused heterocycles such as: glycopyranoso [1,2-d]-1,3-thiazoles, glycopyranoso [1,2-d]-1,3-thiazolidin-2-one or 2-thione have been prepared using *trans*-2-deoxy-2-iodoglycopyranosyl isothiocyanates.[51] Preparation of the 2-deoxy-2-iodoglycopyranosyl isothiocyanate was achieved via electrophilic addition of iodine (I) thiocyanate generated in situ from silica supported KSCN and iodine to the glycal. The *trans*-2-deoxy-2-iodoglycopyranosyl isothiocyanates were obtained exclusively and were further reacted with *O*-and *S*- nucleophiles leading to the formation of the 2-deoxy-2-iodoglycopyranosyl thiocarbamate and dithiocarbamates. These intermediates underwent internal nucleophilic displacement when treated with base (DBU or sodium methoxide) allowing for the formation of the thiazoles **51** (Scheme 17). Direct formation of 2-aminoglycopyranoso thiazoles was also achieved without isolation of the intermediate thioureas when amines or polyamines were used as *N*-nucleophiles.

Isothiocyanates have also been used in the construction of pyrimidine nucleoside based analogues via a [4+2] cycloaddition reaction.[52] The cycloaddition reaction was accomplished using various glycosyl isothiocyanates (pyranoses, furanoses, and disaccharides) in the presence of a diazadienium iodide (Scheme 18). This methodology allowed for the preparation of various pyrimidine nucleoside analogs with total regiocontrol.



Scheme 18. Preparation of pyrimidine nucleoside from isothiocyanates.

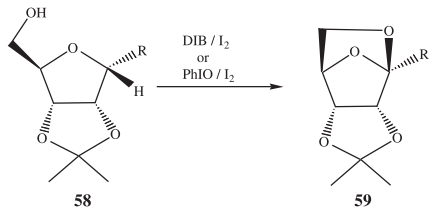
Iodine has also been used in the construction of pseudo-oligosaccharides with potential applications as carbohydrate mimetics.[53] Lay et al. were able to construct disaccharides linked by both a six-membered ring pyran and a five-membered ring furan using either a straight-forward cross-methathesis or a two step procedure (self methathesis followed by cross methathesis). Two monosaccharides were linked by five and six membered rings, via cross-methathesis, employing as a key intermediate a monosaccharide equipped with a homoallylic alcohol functionality and a series of glucose based olefins. The tricyclic pseudo-disaccharides were constructed via electrophilic activation of the olefins using I_2/THF in the presence of $NaHCO_3$ (Scheme 19). The iodocyclization reactions led to the formation of both *R*- and *S*-stereoisomers with poor stereoselectivity. Further investigation to explore the behavior of different electrophilic promoters is currently ongoing.



Scheme 19. Preparation of pseudo-saccharides via an iodocyclization reaction.

A series of carbohydrate based heterocyclic compounds have also been obtained via intramolecular glycosylation reactions involving a hydrogen abstraction from the anomeric carbon of *C*-glycosides. Suarez et al. applied this methodology toward the synthesis of 6, 8-dioxabicyclo[3.2.1]octane and 2,7-dioxabicyclo [2.2.1] heptane rings using anhydroalditols in the presence of (diacetoxyiodo) benzene or iodosylbenzene under irradiation with an 80-W tungsten filament lamp.[54] Different anhydroalditols were reacted under neutral conditions leading to the formation of the cyclic ethers via an intramolecular hydrogen abstraction reaction. The proposed reaction mechanism involved the formation of an alkoxy radical generated in situ by the reaction of the alcohol at the C-5 (furanose) or C-6 (pyranose) position with (diacetoxyiodo) benzene (DIB) or iodobenzene in the presence of iodine. Intramolecular hydrogen abstraction (IHA) with the anomeric position leads to the formation of a *C*-radical. The newly generated *C*-radical is subsequently oxidized with an excess of reagent to give the oxycarbenium ion, that is, then internally trapped by the nucleophilic alcohol leading to the formation of the ether bridge (Scheme 20).

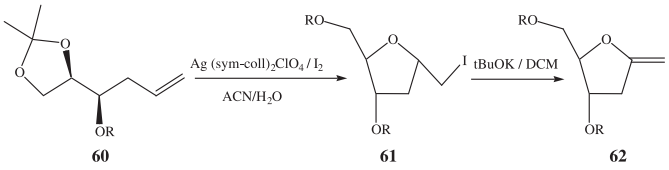
The major advantage of this reaction is that dioxabicyclic alkane ring systems can be constructed under mild conditions compatible with sensitive protecting groups commonly used in carbohydrate synthesis.



Scheme 20. General scheme for the preparation of dioxabicyclo-heptane ring systems.

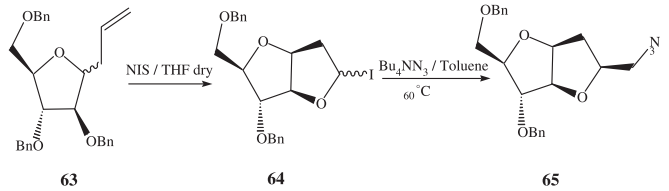
This methodology was extended and used in the synthesis of oxa-azaspirobicyclic systems,[55] imino sugars of the piperidine and pyrrolidine types,[56] chiral vinyl azides and 2H-aziridines.[57]

Endo-glycals have been extensively studied and are valuable intermediates in carbohydrate synthesis. That is not the case with *exo*-glycals, particularly those at positions other than C-1 and C-6, where only a handful of methodologies exist for their construction. Molas et al. reported a stereoselective protocol for the synthesis of 3-deoxy- *exo*-cyclic glycals using 2, 5-disubstituted tetrahydrofurans as starting materials.[58] The substituted tetrahydrofurans were stereoselectively prepared in excellent yields by an iodine-induced cyclization of alkene acetals **60** (Scheme 21). Further elimination of iodine using potassium *tert*-butoxide (KOtBu) allowed for the formation of the final 3-deoxy-furanoid *exo*-glycal **62**.



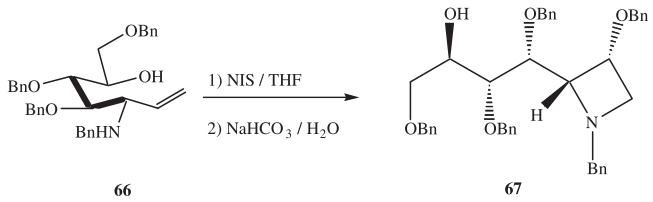
Scheme 21. General scheme for the preparation of 3-deoxy-exo-glycals.

C-glycosides have also been used as starting materials in the preparation of biologically active carbohydrate based bicyclic structures such as sugar azido acids (Scheme 22). The synthesis of these compounds was accomplished through an iodocyclization reaction on *C*-allyl glycosides of D-arabinose using NIS as the source of iodine.[59] The azide residue was reduced and the newly formed amine underwent an amidation reaction with Fmoc-Asp (tBu). The carboxylic acid residue was coupled to a dipeptide (Arg-Gly) using standard peptide chemistry. The final step involved cyclization and formation of a cyclic tripeptide that was found to be a selective antagonist of $\alpha_v\beta_3$ integrins expressed on GM 7373 cells.



Scheme 22. Preparation of sugar azido acids using NIS.

Another example of the use of NIS as the preferred reagent for the introduction of iodine is the work done by Martin et al. in the formation of 1,3-iminoheptitol derivatives.[60] 4, 5, 7-Tri-*O*-benzyl-3-(*N*-benzylacetamido)-1,2,3-trideoxy-D-*gluco*-hept-1-enitol was reacted in the presence of NIS leading to O-alkylation and subsequently to the formation of an oxazoline intermediate. Treatment with $NaHCO_3/H_2O$ lead to the oxazoline ring opening followed by displacement of the iodine and to the formation of the rare class of azetidine containing imino sugar **67** (Scheme 23). This compound was found to be an excellent glycosidase inhibitor.

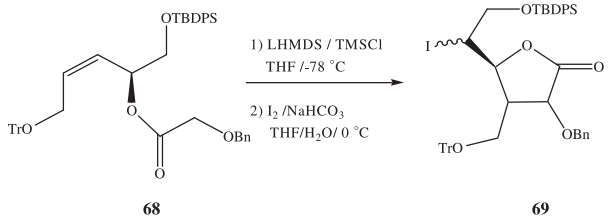


Scheme 23. Preparation of an azetidine containing imino sugar using *N*-iodosuccinimide.

Carbohydrates such as methyl α-D-vicenisaminide have been constructed from non-carbohydrate starting materials via an iodocyclization reaction.[61] The iodocyclization step plays a key role in the synthesis since it leads to the formation of a *trans*-2-oxazolidinone, which upon ring opening allows for the introduction of a secondary -OH group. This functional group installation is necessary for the formation of the pyran in the final step of the synthesis.

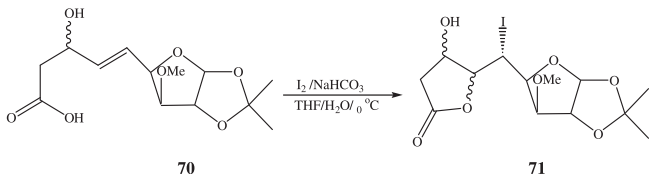
5. Carbohydrate-based lactones

Iodolactonization has been widely used in the synthesis of important functionalized monosaccharides. The synthesis of 3′, 5′-*C*-branched uridine azido acids have been accomplished using an iodolactonization step as key in the reaction (Scheme 24). Cyclization was accomplished using an allylic ester starting material, which was further reacted in the presence of $I_2/NaHCO_3$/THF allowing for the formation of the a mixture of *trans*-lactone and *cis*-lactone, where the *cis*-lactone was the minor product.[62] Ultimately reduction of the carbonyl followed by coupling to 2, 4-O, O′-bis (trimethylsilyl)uracil led to the formation of the uridine azido acid.



Scheme 24. Iodolactonization toward the preparation of racemic branched uridine.

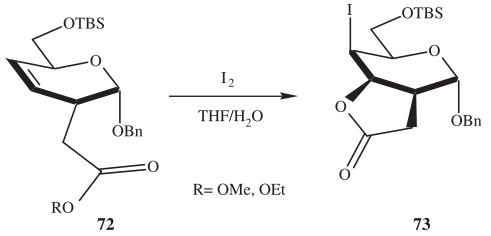
Another example of the use of iodolactonization in the construction of carbohydrate based heterocycles is the work done by Sharma et al. in their syntheses of *C*-linked isoxazolidines.[63] These syntheses were accomplished via the addition of a nitrone to a *C*-linked sugar butenolides. The butenolides in turn were prepared by iodolactonization of a chiral template derived from diacetone glucose (Scheme 25).



Scheme 25. Preparation of *C*-linked butenolide precursors.

Iodolactonization chemistry was also used by Krohn for the preparation of different chiral building blocks using carbohydrates as chiral pools. Specifically, lactones and lactams were formed from the 3,4-unsaturated C-2 branched ester and amide derivatives

(Scheme 26) by treatment with iodine. Of the two cyclization reactions, the best yields were obtained when the amide derivative was used (76%). The resulting intermediates were subjected to several additional transformations leading to the formation of several highly deoxygenated sugars.[64]

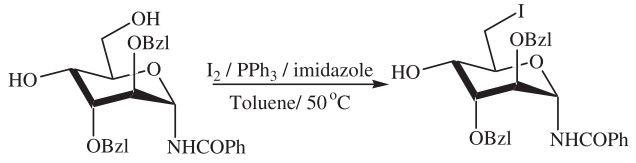


72 73

Scheme 26. Preparation of iodolactones as precursors to deoxygenated sugars.

6. Iodine at C-3, C-4, and C-6 positions

Carbohydrate chemists have taken advantage of the ability of iodine to undergo elimination and nucleophilic displacement in the preparation of complex oligosaccharides. They have done so by constructing monosaccharide building blocks bearing iodine at various positions other than C-2. Iodine at C-6 has been widely used in the preparation of analogues of biologically active carbohydrate compounds such as Sialyl Lewis X (SLeX).[65] In this particular study, iodine was introduced at the C-6 position employing a Garegg–Samuelsson method of alkoxyphosphonium substitution (I_2, triphenylphosphine and imidazole) (Scheme 27). Further elimination of the C-6 iodine **74** led to the formation of the olefin which was then subjected to reduction using H_2/Pd/C. This series of steps allowed for the formation of a hydroxylated pyrrolidine, a key building block in the total synthesis of the oligosaccharide.



74 75

Scheme 27. Preparation of 6-deoxy-6-iodosugars using the Garegg–Sammuelson method.

Nucleophilic displacement of C-6 iodo sugars has also been used in the construction of novel β-1→6-thio-linked cycloglucopyranosides.[66] A key step in the construction of these cyclic oligosaccharides involves the reaction of a 6-deoxy-6-iodo glycoside with a C-1 thiolate anion. Introduction of the iodine at C-6 was accomplished using the same Garegg–Samuelsson methodology previously described. Ultimately, displacement of the iodine by a thioacetate group allowed for the formation of the longer linear thiooligosaccharide. This thiooligosaccharide was then subjected to cyclization leading to the exclusive formation of the β-1→6-thio-linked oligosaccharide.

By far, the use of I_2/Ph_3P/imidazole in various solvents is the most widely used set of conditions for the introduction of iodine at various positions in the sugar including C-4 and C-3.[67–72] Another reagent used for the introduction of iodine at the C-6 position of carbohydrates is NaI. Iodine is readily introduced with this reagent in a polar solvent, such as acetone, under refluxing conditions. Reaction of the C-6 sugar hydroxyl group with mesyl chloride followed by nucleophilic displacement with NaI in refluxing acetone afforded good yields of the C-6 iodide. This procedure was used as an alternative to the I_2/Ph_3P/imidazole conditions and avoided the problem associated with the separation of the triphenylphosphine oxide byproduct from the reaction mixture. Sodium iodide was also used by Bundle et al. in the construction of D-*xylo* and D-*ribo*-phytosphingosines from methyl-2-amino-2-deoxy-β-D-hexopyranosides.[73]

Alternatives to NaI include the use of KI. This was the reagent of choice for the introduction of iodine at the C-4 position by Lee et al. in the synthesis of 4,1′,6′-trihalodeoxy sucrose analogs.[74] Iodine has also been introduced at the C-3 position of 2,3-mannoepoxy-β-cyclodextrin using LiI/Me_3N·HCl/H_2O at 80 °C.[75] Although the yields were low, it is nevertheless an alternative for the introduction of iodine at a considerably less reactive carbon such as C-3.

7. Conclusions

Molecular iodine, iodine salts, and organic sources of iodine are versatile reagents for the transformation of carbohydrates into iodo sugars. Incorporation of iodine into sugars allows for the formation of useful intermediates that can undergo a variety of ionic, free radical and organometallic-based transformations to make useful and biologically-active molecules.

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Biographical sketch

Cecilia H. Marzabadi received her Ph.D. in 1994 from the University of Missouri-St. Louis under the supervision of Professor Christopher Spilling. Following completion of her degree, she pursued post-doctoral training at Hunter College—CUNY working with Professor Richard Franck in the area of 2-deoxyglycoside synthesis. In 1999, she accepted a position as a Clare Boothe Luce Assistant Professor in the Department of Chemistry and Biochemistry at Seton Hall University in South Orange, New Jersey. In 2005, she was promoted to Associate Professor. She is currently the Director of Graduate Studies and the Associate Chair in the Department of Chemistry and Biochemistry at Seton Hall. Her research interests include the synthesis of carbohydrate-based heterocycles and the synthesis of biologically-active sugars for the treatment of a range of disorders.

Michael De Castro was born in Havana, Cuba and immigrated to the United States in 1996. He completed his B.Sc. in Chemistry at Bloomfield College, Bloomfield, New Jersey in 2001. Soon after, he began his Ph.D. studies under the supervision of Dr. Cecilia H. Marzabadi at Seton Hall University, South Orange, New Jersey. His thesis work focused on the development of a new methodology for the preparation of glycosylamides and their use as precursors in the construction of carbohydrate-based heterocycles. Upon receiving his Doctorate in 2006, he joined Dr. Geert-Jan Boons's laboratory at the University of Georgia-Complex Carbohydrate Research Center as a Postdoctoral Associate. There he worked in the development and synthesis of immune adjuvants toward the construction of a novel three-component *anti*-cancer carbohydrate based vaccine. Dr. De Castro is currently an Assistant Professor in the Chemistry Department at Farmingdale State College-State University of New York. His recent research interest revolves around studying the role and functions of complex oligosaccharides in the human immune system as well as the synthesis and development of carbohydrate-based drugs.