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THE DAWN, EVOLUTION AND PERSONAL REMINISCENCES IN STUDIES OF GLYCOSYL ISOCYANATES AND ISOCYANIDES

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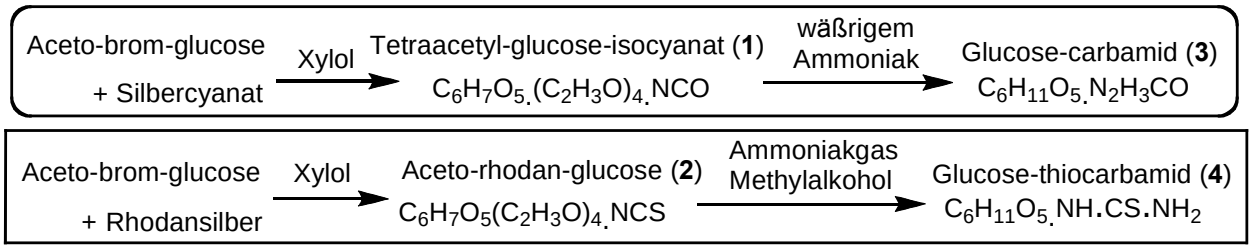
Abstract – Historical background and personal reflections on my research career studying glycosyl isocyanates and isocyanides are described.

CONTENTS

1. INTRODUCTION

1-1. Historical Background of Glucopyranosyl Isocyanate

In 1914, Emil Fischer reported the synthesis of glucosyl isocyanate **1** (Tetraacetyl-glucose-isocyanat) and its thio-counterpart, glucosyl isothiocyanate **2** (Aceto-rhodan-glucose) in a paper entitled "Synthese neuer Glucoside" (Scheme 1).[1] The classical Fischer's synthesis of glucosyl isocyanate **1** and isothiocyanate **2** involves respective treatment of tetraacetylglucosyl bromide with either silver cyanate (Silbercyanat: AgOCN) and silver thiocyanate (Rhodansilber: AgSCN) in xylene (Xylol). Furthermore, reaction of glucosyl isocyanate with aqueous ammonia resulted in the formation of glucosyl urea **3** (Glucose-carbamid). Similarly, reaction of glucosyl isothiocyanate **2** with ammonia in methanol furnished glucosyl thiourea **4** (Glucose-thiocarbamid). Glucosyl urea **3** proved to be identical to the product (Glucose-harnstoff or carbamide duglucose) reported by Schoorl in a 1903 paper entitled "Les uréides (carbamides) des sucres". Schoorl examined the acid-catalyzed condensation of D-glucose with urea to find the formation of glucosyl urea **3**.[2]



Scheme 1. Fischer's Synthesis of Glucosyl Isocyanate, Isothiocyanate, Urea and Thiourea

Although the straight-chain structure of glucosyl urea was advanced by Schoorl, the pyranosyl structures with a β-configuration of the glucosyl urea **3** and thiourea **4** (Figure 1) were assigned later based on the chemical transformations (acetylation, sodium metaperiodate oxidation and deamination by nitrous acid)[3] and synthetic studies of pyrimidine nucleosides starting with **3** and **4**.[4] As a result, the structures of glucosyl isocyanate and isothiocyanate synthesized by Fischer are now assumed to be the corresponding β-glucopyranosyl (GP) structures as represented in Figure 1.[5]

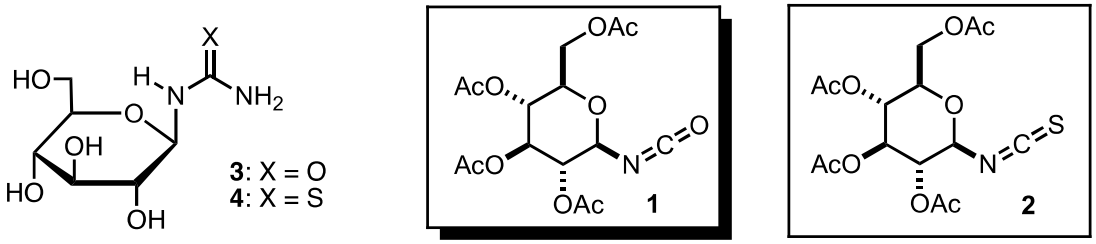


Figure 1. β-Pyranosyl Structures of Glucosyl Urea, Thiourea, Isocyanate and Isothiocyanate

While the record of Fischer's contribution to the field of carbohydrate chemistry is stunning,[6] his first synthesis of β-GP isocyanate **1** is overshadowed by his great monumental work to determine the configuration of hexoses. Moreover, β-GP isothiocyanate **2** secures its widespread use in both the syntheses of nucleoside analogs and glycoconjugates.[7] In contrast, chemistry of β-GP isocyanate **1** has gone through a long, more than 80-year stagnation phase in its evolution. The long-standing lack of interest in β-GP isocyanate **1** may be partially a result of the inconvenience associated with preparation and handling caused by its highly reactive nature. For example, β-GP isothiocyanate **2** is sufficiently stable to purify by silica-gel chromatography,[8] whereas β-GP isocyanate **1** does not survive under such purification conditions. Accordingly, Fischer's synthesis of β-GP isocyanate **1** has been reported to be difficult to reproduce.[9]

At the beginning of the 21st century, the chemistry of GP isocyanates flourished, and during this period, three new and reliable methods for the synthesis of GP isocyanates were developed by Ichikawa and his co-workers. The first procedure involves reaction of β-GP amine with triphosgene (coined as the 'triphosgene method'). The second protocol involves oxidation of GP isocyanides (isocyanide method), the development of which led to the first stereospecific synthesis of both α-and β-GP isocyanates. The third approach employs elimination reaction of GP carbamates (carbamate method).

1-2. How did I Get Involved in the Chemistry of Glucopyranosyl Isocyanate

My passion for GP isocyanate originated in endeavors aimed at the total synthesis of glycocinnasperimicin D (**5**), a member of a family of glycocinnamoylspermidine antibiotics (Figure 2).[10] The aminosugar antibiotic **5** was isolated from the fermentation broth of *Nocardia* strain by Umezawa and his co-workers. Ellestad and his co-workers reported the isolation of the more complex congener, LL-BM123β (**6**).[11] One of the most unique structural features of these aminosugar antibiotics is the urea glycoside linkage. In the structure of glycocinnasperimicin D (**5**), the urea linkage connects two unusual amino sugars, 2-ureido-pentose and 2-guanidino-4-ureido-6-deoxy-α-D-glucopyranose, via a β-configuration, while the corresponding anomeric center in LL-BM123β (**6**) is assigned to have an α-configuration.[12]

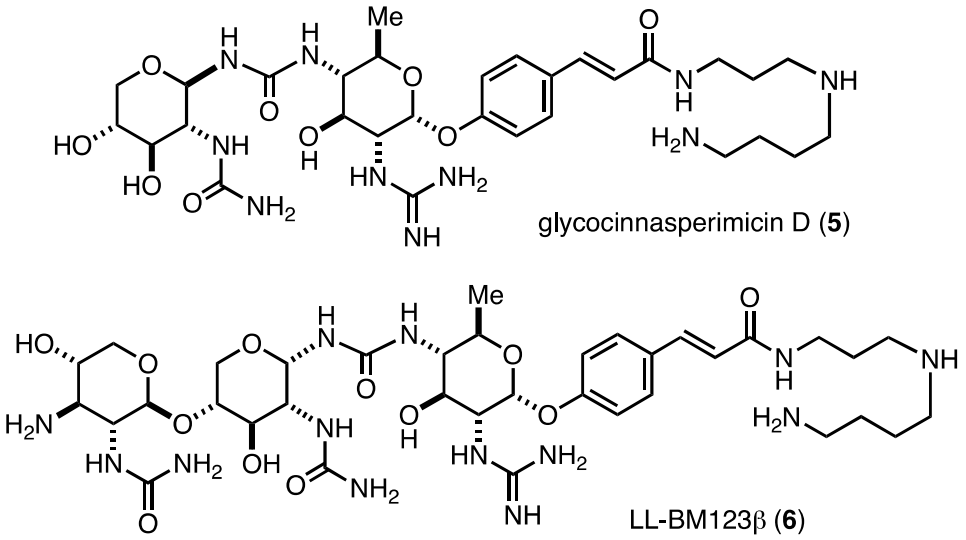
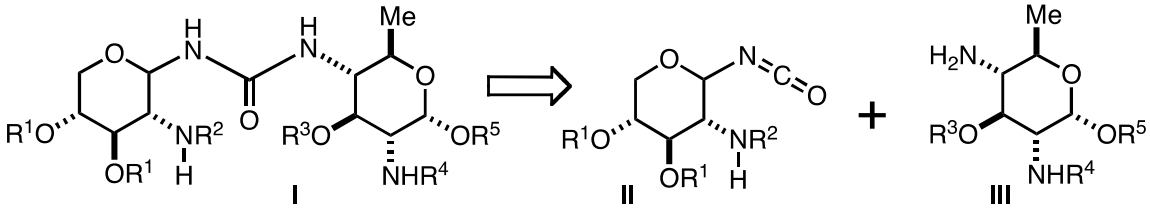


Figure 2. Glycocinnamoylspermidine Antibiotics

The most difficult and challenging problem inherent in the synthesis of **5** is the construction of the urea-glycosyl bond. In designing a strategy for construction of the urea glycosyl bond, I envisioned that the reaction of glycosyl isocyanate **II** with aminosugar **III** would afford the desired urea glycoside **I** (Scheme 2).



Scheme 2. Retrosynthetic Analysis of Urea Glycosyl Bond

Initial probing the viability of this approach focused on the synthesis of α- and β-GP isocyanates as simple model compounds and their reactions with amines which would lead to the corresponding α- and β-GP ureas. In a survey of the literature to collect information about GP isocyanates and ureas, I found that in the early 20th century Emil Fischer reported the synthesis of β-GP isocyanate **1**.[1] Moreover, although several syntheses of α- and β-GP isothiocyanates have been described,[13] no report exists about the synthesis of α-GP isocyanate and α-GP urea. Fischer's synthesis of β-GP isocyanate **1** is a really amazing chemistry, falling into the pre-UV, -IR and -NMR age, often mocked now as a kind of prehistory of chemistry.[14] From the textbook of organic chemistry, Emil Fischer descended in front of a middle-aged (mentally young) Japanese organic chemist (Y. I.). I confess that the marvelous nature of Fischer's β-GP isocyanate synthesis was the revelation that stimulated me to secure an unexplored, potentially promising and rich (I dreamed at that time) field of research work.

Two retrosynthetic schemes for the synthesis of GP isocyanates came into my mind at that time (Figure 3). The classical Fischer synthesis of β-GP isocyanate corresponds to the strategy using disconnection at bond ***a***. The retrosynthesis analysis, involving bond ***b*** disconnection, is the strategy reflected in the triphosgene method in which GP amine reacts with a phosgene equivalent.[15] Disconnection at bond ***c*** corresponds to the isocyanide method which relies on an oxidation reaction of GP isocyanide. With these retrosynthetic analyses in mind, I launched a journey aimed at the total synthesis of glycocinnasperimicin D with a bright undergraduate student, Taihei Nishiyama. Nishiyama worked with me for six years and accomplished the first total synthesis of glycocinnasperimicin D, which became the basis of his PhD thesis.

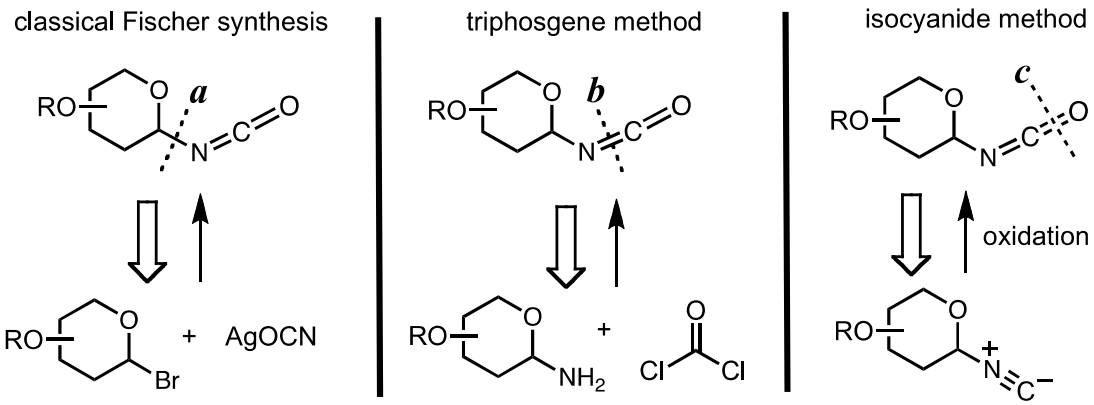


Figure 3. Retrosynthetic Analysis of Glycopyranosyl Isocyanate

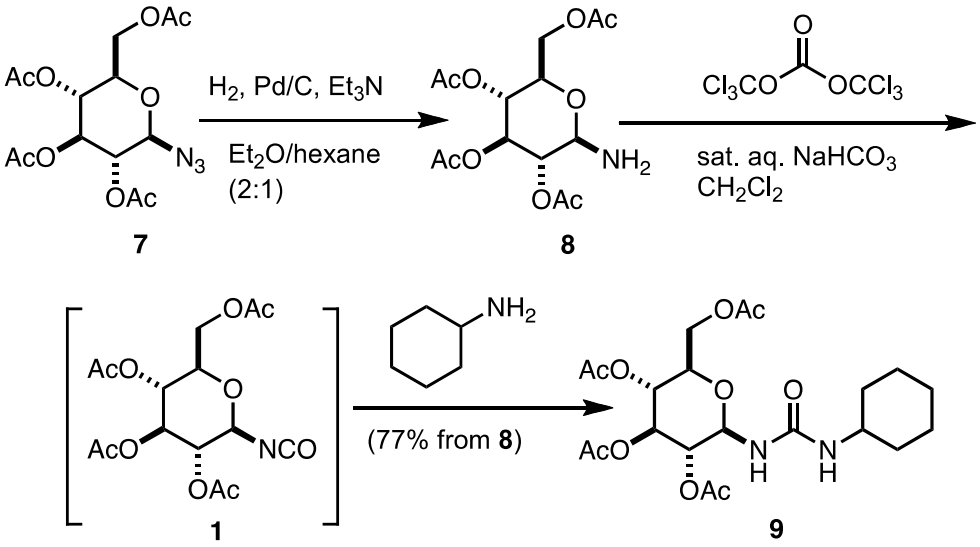
In this review, I would like to trace the evolution and development of our long and fruitful journey of the research endeavaors focusing on GP isocyanates and isocyanides, which led to the urea- and carbamate-tethered glycoconjugate synthesis protocol and the total synthesis of glycocinnasperimicin D.

2. TRIPHOSGENE METHOD FOR THE PREPARATION OF β-GLUCOPYRANOSYL ISOCYANATE

2-1. In Situ Generation of β-Glucopyranosyl Isocyanate

Our initial approach for the synthesis of GP isocyanates is based on the reaction of GP amine with triphosgene, which is a safe and crystalline synthetic equivalent of dangerous, risky and highly toxic gaseous phosgene.[16] This process led to the successful in situ generation of β-GP isocyanate and its transformation into a variety of β-GP ureas (Scheme 3).[17] In the event, a two-phase mixture consisting of a solution of β-GP amine **8**, prepared by catalytic hydrogenation of β-GP azide **7**, and triphosgene in dichloromethane and aqueous sodium hydrogen carbonate was vigorously stirred at room temperature for 30 minutes under Schotten-Baumann conditions. The organic layer was separated, dried (Na_2SO_4) and then treated with cyclohexylamine. After work-up and purification by chromatography, the β-GP urea **9**

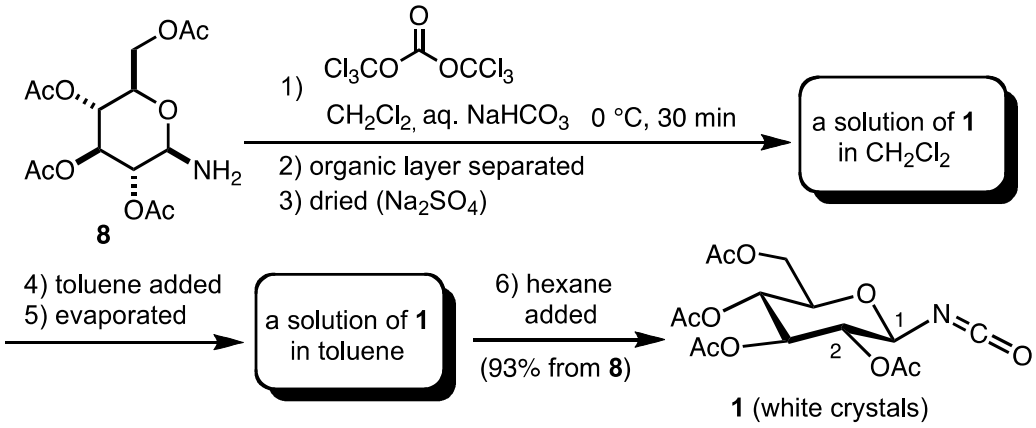
was obtained in 77% yield. In this reaction sequence, isolation of β-GP isocyanate **1** was avoided because of its anticipated highly reactive nature. Actually, initial attempts to isolate and purify β-GP isocyanate were unsuccessful.



Scheme 3. Triphosgene Method for the Synthesis of β-Glucopyranosyl Isocyanate

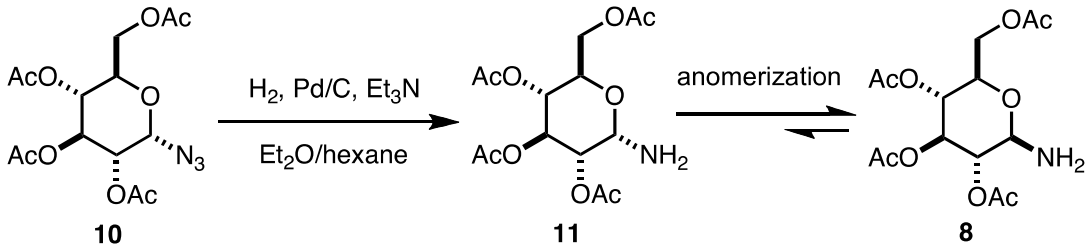
2-2. Isolation of β-Glucopyranosyl Isocyanate as White Crystals

Performing collaborative studies with gifted and enthusiastic students like Yohei Matsukawa is a privilege. He joined our research project as an undergraduate student and worked with me for three years, which led to his co-authorship of seven publications. Matsukawa has excellent experimental skills that enabled him to develop a convenient method for the preparation and isolation of Fischer's β-GP isocyanate **1** (Scheme 4).[18] The heart in this synthesis is the direct isolation of β-GP isocyanate by crystallization from a mixture of toluene and hexane, which avoided the problematic aqueous work-up and suppressed hydrolysis of isocyanate function. As a result, we succeeded in isolation of pure β-GP isocyanate **1** as white crystals in an excellent yield (93%). The melting point and specific rotation of the crystals **1** were found to be 118–120 °C and $[\alpha]^{29}_{D} = -6.7$ (*c* 1.00, $CHCl_3$), which are consistent with those reported by Fischer[1] (mp 117–118 °C and $[\alpha]^{19}_{D} = -7.38$ (*c* 1.0, $Cl_2CHCHCl_2$). Our assignment of anomeric configuration of β-GP isocyanate **1** was carried out by using ^{1}H NMR spectroscopy, which confirmed the existence of β-stereochemistry through analysis of the anomeric hydrogen coupling constant ($J_{1,2}$ = 9.5 Hz). Following our ^{1}H NMR characterization of the β-stereochemistry, Schotten reported a conclusive X-ray analysis of Fischer's β-GP isocyanate **1**.[19]



Scheme 4. Isolation of β-Glucopyranosyl Isocyanate as White Crystals

In contrast to the preparation of β-GP isocyanate **1**, the synthesis of α-stereoisomer was fraught with difficulties (Scheme 5). Many attempts at catalytic hydrogenation of α-GP azide **10** under a variety of conditions in order to prepare α-GP amine **11** afforded a mixture of **11** and **8**. Furthermore, the α-amine **11** rapidly isomerized to produce the thermodynamically stable β-amine **8** during isolation. Since α-amine **11** is inclined to isomerize into β-amine **8**, we concluded that a more stable precursor for the preparation of α-GP isocyanate was needed. This consideration led us to develop a second method for the synthesis of α-GP isocyanate that relies on the use of the α-GP isocyanide (see the next section 3).



Scheme 5. Unsuccessful Attempts to Synthesize α-Glucopyranosyl Isocyanate

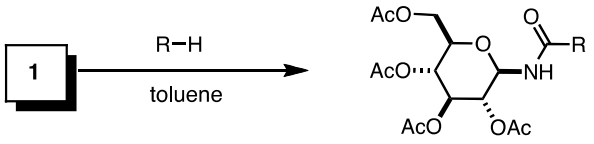
2-3. Glycoconjugate Synthesis Using Fischer's Glucopyranosyl Isocyanate

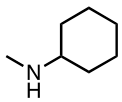
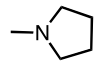
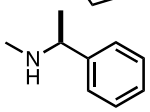
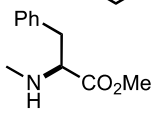
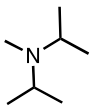
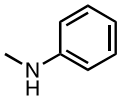
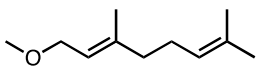
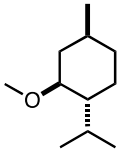
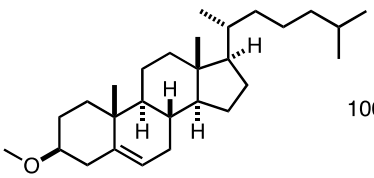
The development of a new method for anchoring carbohydrate moieties onto biomolecules via nonnative glycosidic linkages to produce glycoconjugates, which is an alternative to glycosylation, has been an active area of numerous research endeavors. Although I was not familiar with this research field, I envisioned that β-GP isocyanate could be a promising synthon for glycoconjugate synthesis. This expectation arouse from the observation that while β-GP isocyanate is prone to hydrolysis (kinetically reactive), it can be stored in a freezer without a noticeable decrease in its reactivity (thermodynamically stable). Beyond a prime interest in total synthesis of glycocinnasperimicin D, I was fascinated by the potential to use β-GP isocyanate to build up urea- and carbamate-tethered glycoconjugates and

pseudooligosaccharides.

As revealed in Table 1, reaction of β-GP isocyanate **1** with amines as well as alcohols proceeded smoothly to afford the corresponding β-GP ureas and carbamates in excellent yields (>89%). The synthetic operations for β-GP ureas (entries 1 to 5) are quite straightforward. Specifically, we observed that simple treatment of amines (1.0 equiv) with **1** (ca. 1.1 equiv) in toluene at room temperature for 60 minutes led to urea glucosidation. After quenching to remove excess **1** by the addition of *N*,*N*-dimethylethylenediamine, the resulting reaction mixture was concentrated and then subjected to

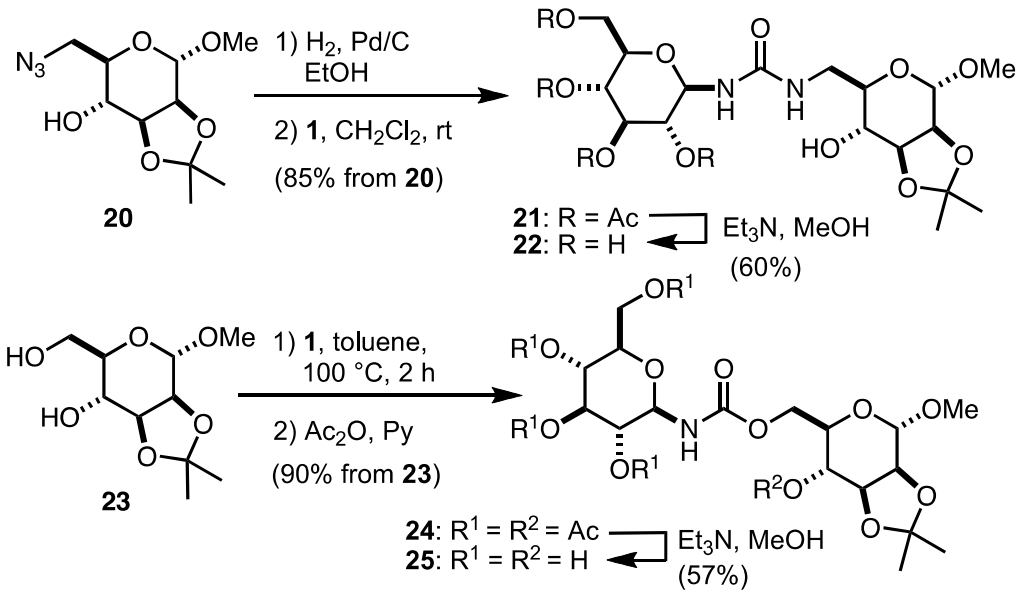
Table 1. Synthesis of Urea- and Carbamate-Tethered Glycoconjugates Using β-Glucopyranosyl Isocyanate



Entry	product (R =)	temperature (°C)	equiv. of **1**	% yield
1	 **9**	rt	1.1	92
2	 **12**	rt	1.1	94
3	 **13**	rt	1.1	90
4	 **14**	rt	1.1	90
5	 **15**	rt	1.1	89
6	 **16**	70	1.1	90
7	 **17**	100	2.0	98
8	 **18**	100	1.5	91
9	 **19**	100	2.0	98

chromatography. Even in the case of a sterically hindered amine, such as diisopropylamine (entry 5), the corresponding β-GP urea **15** was isolated in good yield (89%). When an amine of low nucleophilicity, such as aniline, was employed (entry 6), heating the reaction mixture at 70 °C for 50 minutes furnished β-GP urea **16** in 90% yield. Carbamate-tethered glucosides of terpene alcohols were also prepared as represented in entries 7, 8 and 9. In each case, a slightly excess amount of **1** (1.5 to 2.0 equiv) and heating the reaction mixture at 100 °C for 3 hours led to production of each β-GP carbamate (**17**, **18** and **19**) in satisfactory yields (> 91%).

We further examined the synthesis of urea- and carbamate-tethered disaccharides to expand the synthetic potentiality of β-GP isocyanate **1** (Scheme 6). The synthesis of two disaccharides, **22** and **25**, was achieved by the coupling reaction of **1** with two sugars prepared from mannose. Catalytic hydrogenation of azide **20** gave the corresponding amine, which was subsequently treated with **1** in dichloromethane at room temperature to form urea-tethered disaccharide **21** in 85% yield. Carbamate-tethered disaccharide **24** was also prepared by heating a mixture of **1** and **23** in toluene at 100 °C for 2 hours, followed by acetylation and purification to give **24** in 90% yield. The acetate groups in **21** and **24** were removed by treatment with triethylamine in methanol to furnish the respective urea- and carbamate-tethered disaccharide **22** and **25**.[20]



Scheme 6. Synthesis of Urea- and Carbamate-Tethered Disaccharides

2-4. Fischer's Glucopyranosyl Isocyanate as a Useful Synthon for the Synthesis of Supramolecules

Newkome and his co-workers reported the synthesis of carbohydrate-functionalized terpyridines and examined their self-assembly into twisted nanofibers (Figure 4).[21] β-GP isocyanate **1** was connected with a linker having a free amino group. Deprotection of the resulting precursor **26** led to the formation

of the urea-tethered linear type monomer **27**. The twisted self-organized nanofiber was obtained by simply cooling a homogenous solution of **27** in a suitable ratio of water and methanol from 60 to 20 °C. Molecular modeling studies showed that the hydrophobic terpyridines stacked on the interior of an aggregate surrounded by the hydrocarbon linkers and hydrophilic carbohydrates. Newkome further developed this two-dimensional, terpyridine-based supramolecular spoked wheel into a 3D, bicycle-like wheel.[22]

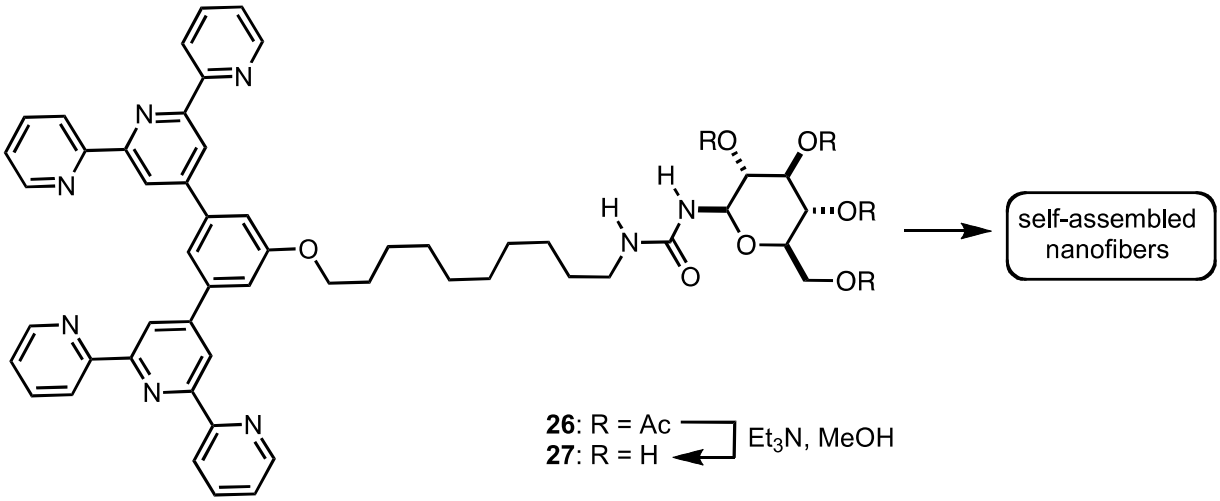


Figure 4. Carbohydrate-Functionalized Terpyridine for Self-Assemble Twisted Nanofibers

Schotten reported the synthesis of the fully fledged phthalocyanine (Pc) **29** using the ex post

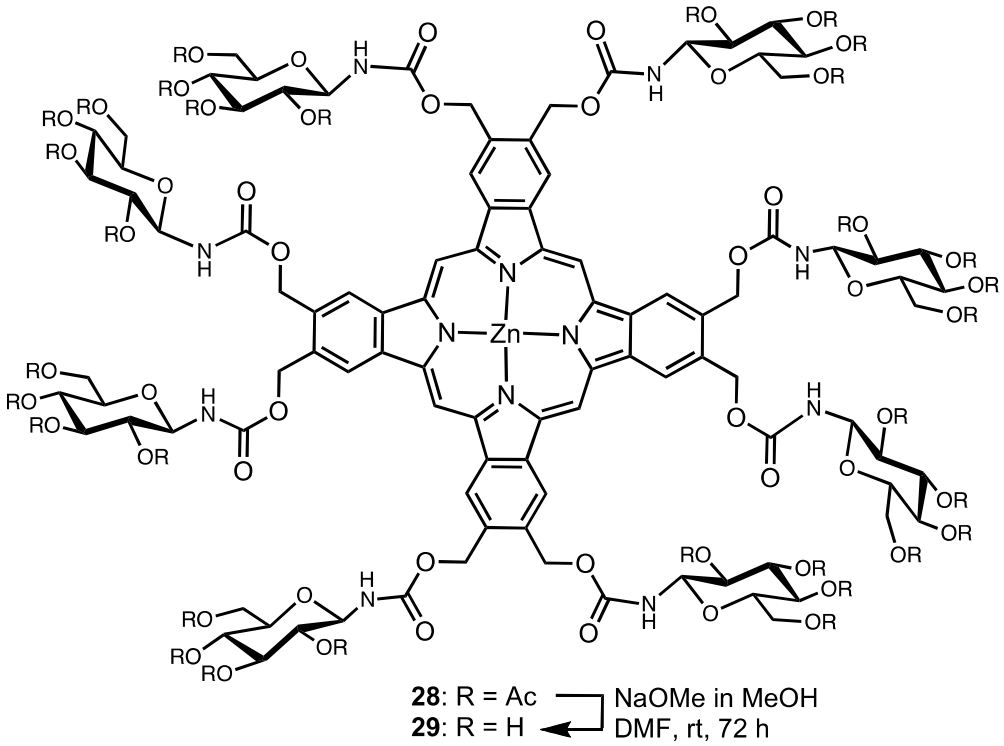


Figure 5. *octa*-Substituted Glycoconjugated Zinc Phthalocyanine

glycoconjugation method (Figure 5).[19] Reaction of Pc scaffold with β-GP isocyanate **1** yielded the *octa*-substituted glycoconjugated ZnPc **28**. Deprotection of the *O*-acetyl-protected carbamoyl glucosyl ZnPc **28** was successfully achieved using Zemplen conditions, in which all carbamate linkages remained intact. As a result, **29** was isolated as a pure uniform substance as proven by ^{1}H and ^{13}C NMR and HRMS.

Dabrowa and Jurczak reported the preparation of the symmetrical and near planar receptor *E*-**30** by using reaction of 4,4'-diaminoazobenzene with β-GP isocyanate **1** (Figure 6).[23] The V-shaped *Z*-**30** receptor was then produced by *E*→*Z* isomerization driven by irradiation with UV light, and spontaneously re-equilibrated with first-order kinetics. The photochemically and thermally interconvertible planar *E*-**30** and concaved *Z*-**30** were found to exhibit different affinities, selectivities, and binding modes toward α-amino acid-derived carboxylates in a highly polar medium, which means that light can be used for switching of the chiral recognition.

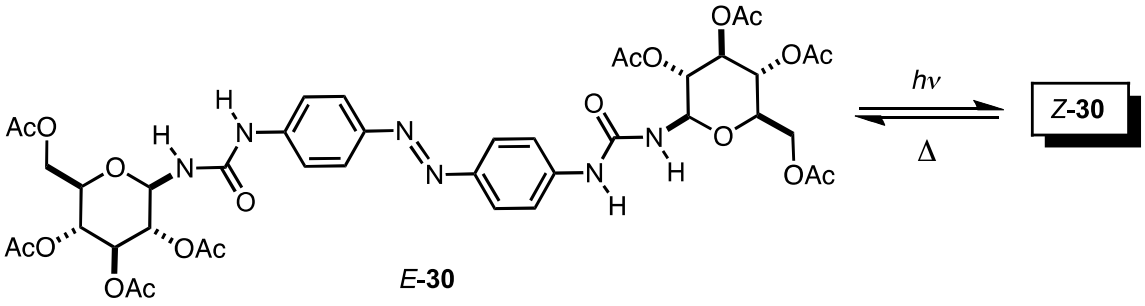
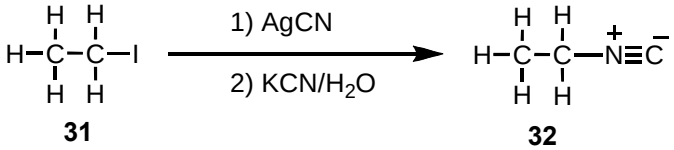


Figure 6. Symmetrical and Near Planar Receptor and its Isomerization

3. ISOCYANIDE METHOD FOR THE PREPARATION OF GLUCOPYRANOSYL ISOCYANATE

3-1. Historical Perspective of Glycosyl Isocyanides

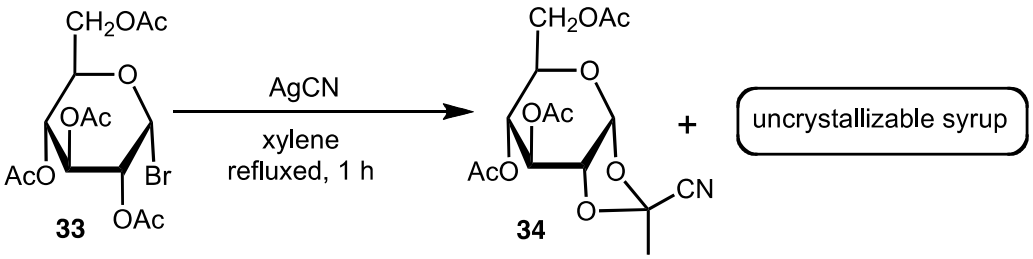
One of the classical method for the synthesis of isocyanides reported by Gautier employs alkylation reactions of alkyl halides with silver cyanide. A typical example shown in Scheme 7 involves reaction of ethyl iodide (**31**) with silver cyanide to form ethyl isocyanide (**32**).[24]



Scheme 7. Synthesis of Ethyl Isocyanide by the Procedure of Gautier

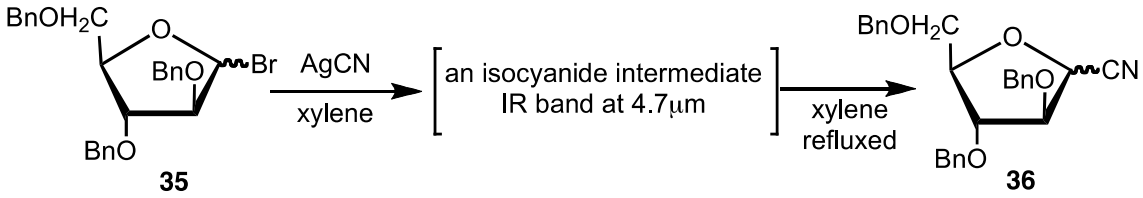
In 1934, Buerger applied this type of reaction in the field of carbohydrate chemistry (Scheme 8).[25] A solution of 2,3,4,6-tetra-*O*-acetyl-α-GP bromide (**33**) and silver cyanide in xylene was heated at reflux for

1 hour.[26] This reaction produced a crystalline substance, which was assigned as '1-cyano-2,3,4,6-tetraacetyl-*d*-glycose'. Buerger observed that the substance did not react with mercuric oxide at 70–80 °C. From this observation, he concluded that the substance was nitrile rather than isocyanide. In 1963, Coxon and Fletcher repeated Buerger's experiment and elucidated the correct structure of the crystalline substance as a 2-cyano-2-methyl-1,3-dioxolane derivative **34**.[27] In addition, Coxon and Fletcher proposed β-GP isocyanide as a hypothetical intermediate in the formation of **34** and noted that 'No evidence of isonitrile formation was found in the condensation of I with silver and mercuric cyanides, although a significant proportion of the condensation product remained unidentified as uncrystallizable sirup'.



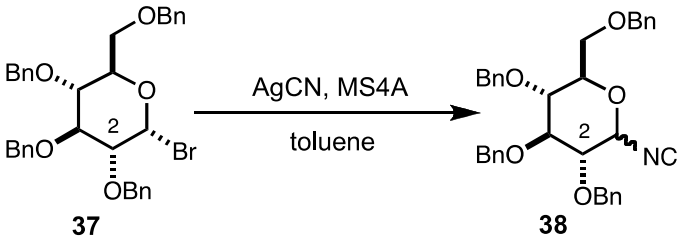
Scheme 8. Reaction of Glucopyranosyl Bromide with Silver Cyanide

In 1974, Acton and his co-workers treated 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl bromide **35** with silver cyanide in xylene (Scheme 9).[28] Although formation of a product containing an isocyanide group was suggested by the observation of a band at 4.7 μm in the IR spectrum of the crude product mixture, heating the mixture at reflux led to production of the thermodynamically more stable cyanide **36**.



Scheme 9. Reaction of Arabinofuranosyl Bromide with Silver Cyanide

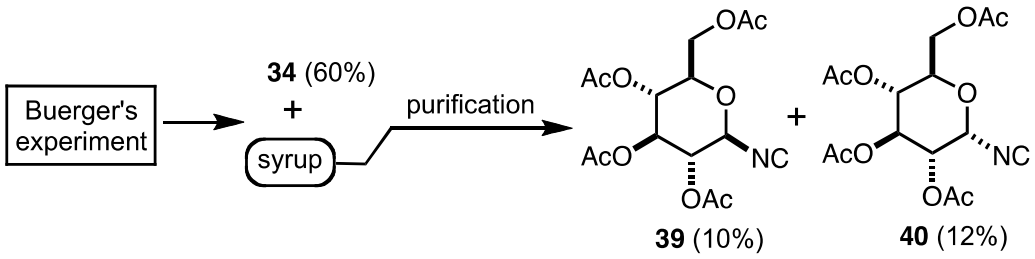
In 1976, Descotes examined the reaction of benzyl-protected α-GP bromide **37** with silver cyanide in order to avoid the participation of the neighboring acetyl group at C-2 (Scheme 10).[29] The reaction of **37** with freshly prepared silver cyanide in the presence of molecular sieves 4A in toluene at room temperature for 36 hours resulted in the formation of a mixture of α- and β-isocyanides **38**.



37 38

Scheme 10. Isolation of Glucosyl Isocyanides as a Mixture of Anomers

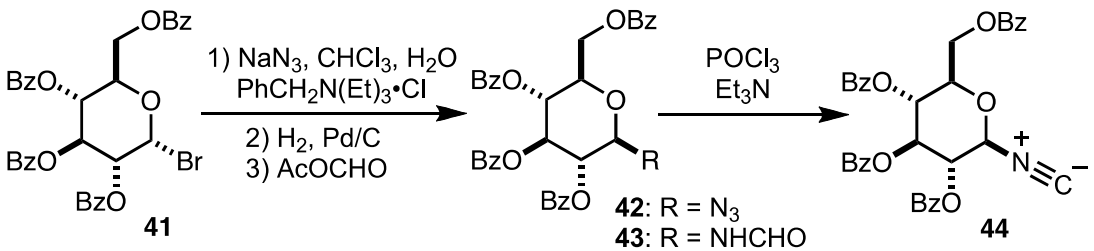
In 1977, Martin-Lomas reexamined the Buerger's experiment, and purified the products by silica-gel chromatography and repeated recrystallization from ethanol.[30] Although **34** was found to be a major product formed in 60% yield, β- and α-GP isocyanides **39** and **40** were also isolated as crystals in 10% and 12% yield, respectably.



39 (10%) **40** (12%)

Scheme 11. Isolation of α- and β-Glucopyranosyl Isocyanides

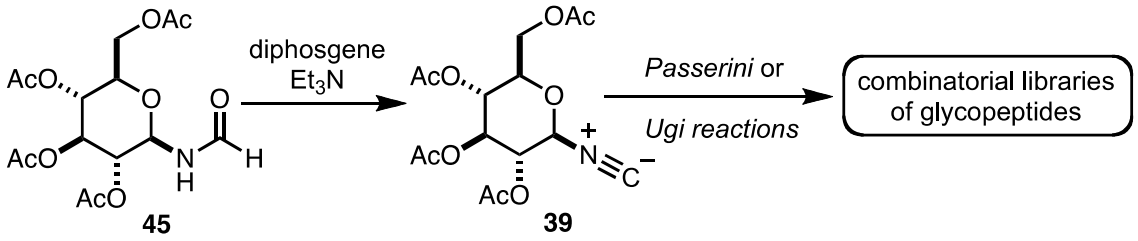
In 1978, a more convenient method for the preparation of β-GP isocyanide was developed by Zwikker (Scheme 12).[31] Nucleophilic displacement reaction of α-GP bromide **41** with sodium azide gave β-GP azide **42** quantitatively. Catalytic hydrogenation of β-GP azide **42** followed by formylation of the produced β-GP-amine afforded β-GP formamide **43**. Dehydration of formamide **43** by treatment with phosphorus oxychloride and triethylamine furnished β-GP isocyanide **44**, which was used in a polymerization reaction to synthesize rod polymers with a helical configuration.



41 **42**: R = N_3 **43**: R = NHCHO **44**

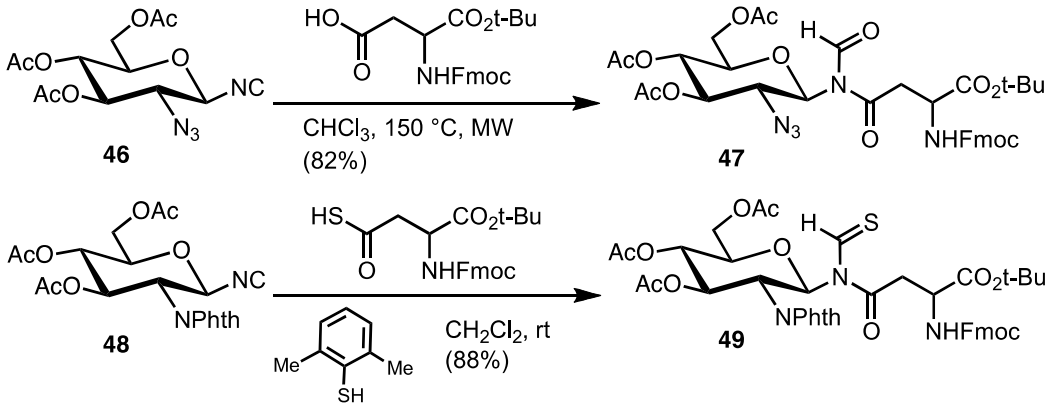
Scheme 12. Synthesis of β-Glucopyranosyl Isocyanide by Dehydration of β-Glucopyranosyl Formamide

Ziegler prepared tetraacetyl β-GP isocyanide **39** using a modified method devised by Zwikker, in which diphosgene was used for dehydration of β-GP formamide **45** (Scheme 13). Ziegler further exploited Passerini and Ugi reactions of β-GP isocyanide **39** for the synthesis of combinatorial libraries of glycopeptides.[32]



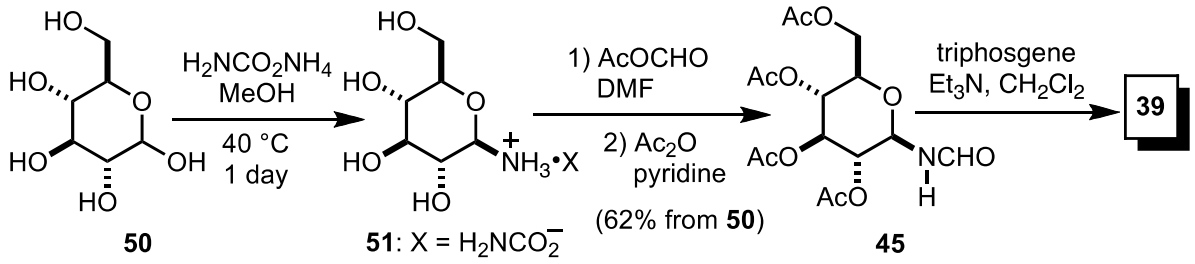
Scheme 13. Passerini and Ugi Reactions of β-Glucopyranosyl Isocyanide

Applications of glycosyl isocyanides to the syntheses of glycosyl amino acid conjugates were reported by Danishefsky (Scheme 14). Two-component coupling reaction of the mono-saccharide isocyanide **46** with Fmoc-protected asparatic acid promoted by microwave heating at 150 °C provided *N*-formyl glycosyl amino acid **47** in 82% yield.[33] This process required use of the azide-protected glucosamine isocyanide **46** and harsh microwave conditions. However, a modified protocol using phthalimide-protected glucosamine isocyanide **48** and aspartic thioacid in the presence of bulky 2,6-dimethylthiophenol as activator at room temperature was found to afford *N*-thioformyl product **49** in 88% yield.[34]



Scheme 14. Synthesis of *N*-Linked Glycosyl Amino Acid Conjugates

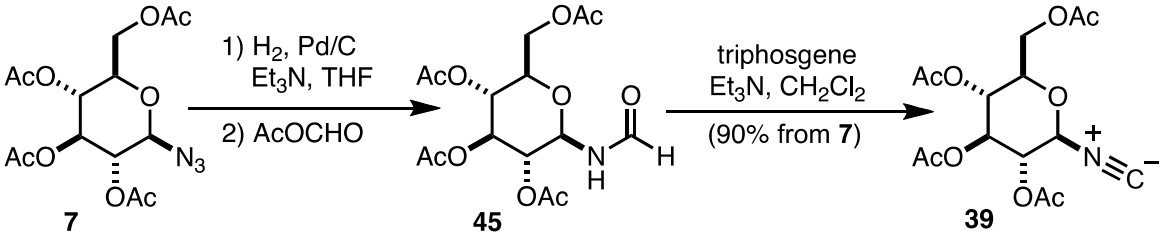
In 2016, we reported a new approach to the synthesis of β-GP isocyanide **39** (Scheme 15).[35] The crucial step in this pathway is *N*-glycosylation of unprotected D-glucose to form β-GP formamide (**50**→**51**→**45**). The main advantages of this method lie in its experimental simplicity, use of inexpensive reagents and avoidance of the use of unstable GP halide intermediate, which enabled a convenient gram-scale synthesis of β-GP isocyanide **39**.



Scheme 15. Synthesis of β-Glucopyranosyl Isocyanide through *N*-Glycosylation of Unprotected D-Glucose

3-2. Stereospecific Synthesis of an Anomeric Pair of Glucopyranosyl Isocyanates and Ureas

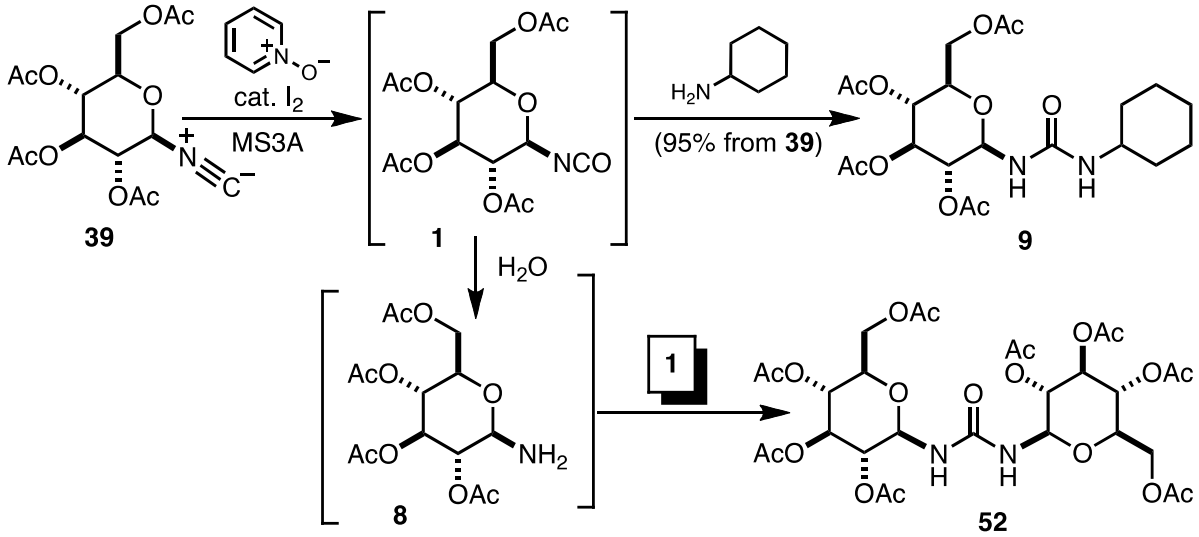
I was inspired by the report of Martin-Lomas, which showed that α- and β-GP isocyanides can be isolated as crystals with stable anomeric stereochemistries. With this crucial information coupled with retrosynthetic analysis for the synthesis of GP isocyanates (Figure 3, isocyanide method) in mind, we planned to oxidize α- and β-GP-isocyanides to generate the corresponding α- and β-GP isocyanates and ureas.[36] Specifically, I hoped that oxidation of α-GP isocyanide would lead to stereospecific production of α-GP isocyanate and urea. Initial efforts to explore isocyanide method focused on the synthesis of β-GP isocyanide **39**, which was conveniently prepared by using a modification of the method reported by Zwikker (Scheme 16). Catalytic hydrogenation of β-azide **7** followed by in situ formylation gave β-GP formamide **45**. Dehydration of β-GP formamide **45** with triphosgene in the presence of triethylamine gave β-GP isocyanide **39** in 90% overall yield from β-GP azide **7**.



Scheme 16. Synthesis of β-Glucopyranosyl Isocyanide

Although we planned to synthesize β-GP isocyanate **1** by oxidation of β-GP isocyanide **39**, it was expected that isolation of the produced β-GP isocyanate using aqueous work-up would be troublesome. In order to circumvent this problem, we explored a one-pot process, comprised of oxidation of β-GP isocyanide **39** followed by conversion of the in-situ generated β-GP isocyanate **1** to the corresponding urea by the reaction with amine. After screening a number of oxidizing reagents, we found that use of pyridine *N*-oxide and a catalytic amount of iodine in acetonitrile was the most satisfactory condition

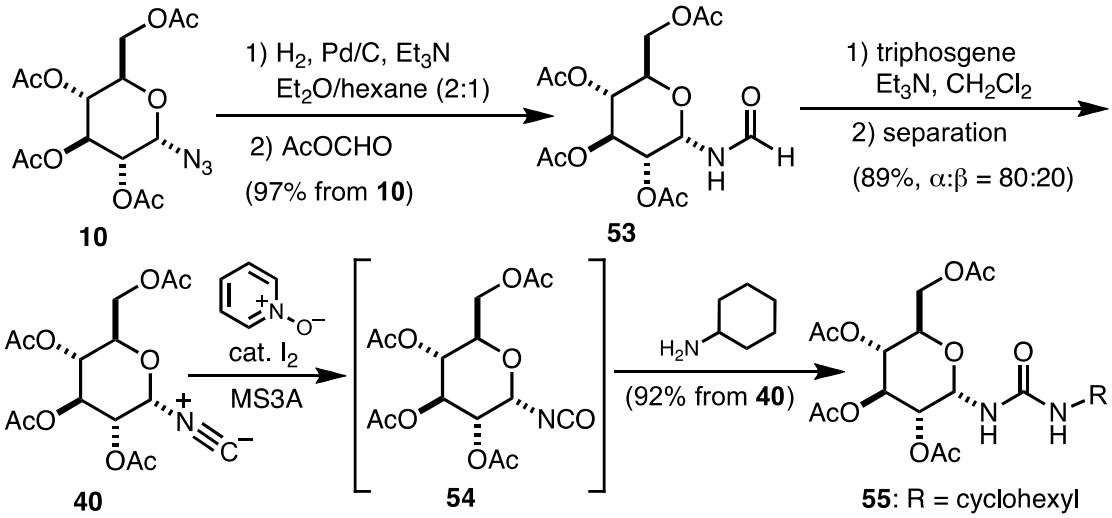
(Scheme 17).[37] Accordingly, oxidation of β-GP isocyanide **39** at room temperature for 30 minutes proceeded smoothly and subsequent addition of cyclohexylamine to the resulting reaction mixture converted the in-situ generated β-GP isocyanate **1** into the stable β-GP urea **9**. It should be noted that we often observed formation of a considerable amount of *N,N*'-di-β□β-D-GP urea **52** as a by-product, which likely arose from hydrolysis of the moisture sensitive β-GP isocyanate **1** to give β-GP amine **8** which subsequently reacted with β-GP isocyanate **1** to afford **52**. The formation of this unwanted product was finally suppressed by addition of molecular sieves 3A in the reaction mixture as water scavenger, leading to reproducible and higher yields of β-GP urea **9**.



Scheme 17. Isocyanide Method for the Preparation of β-GP Isocyanate and Urea

Encouraged by the success of the oxidation reaction of β-GP isocyanide, we next examined the preparation of α-GP isocyanide **40** and its transformation to α-GP isocyanate and corresponding urea (Scheme 18). The synthesis of α-GP isocyanide **40** began with catalytic hydrogenation of α-GP azide **10** followed by immediate treatment of the labile α-GP amine with acetic formic anhydride to form a mixture of α-GP formamide **53** and the β-anomer **45**. Treatment of this mixture with triphosgene and triethylamine and separation of the products by silica-gel chromatography furnished an 89% yield of α-GP isocyanide **40** and β-**39** in a ratio of 80:20. Formation of α-GP isocyanate **54** and its transformation to α-GP urea **55** was accomplished using conditions similar to those given in Scheme 17. We were very pleased to find that ^{1}H NMR analysis of the crude product mixture confirmed that no β-GP urea had formed. This result demonstrated that oxidation of α-GP isocyanide **40** proceeded with retention of the configuration at the anomeric position and that the resulting α-GP isocyanate **54** was configurationally stable so that it reacted with cyclohexylamine to provide α-GP urea **55**. Purification of

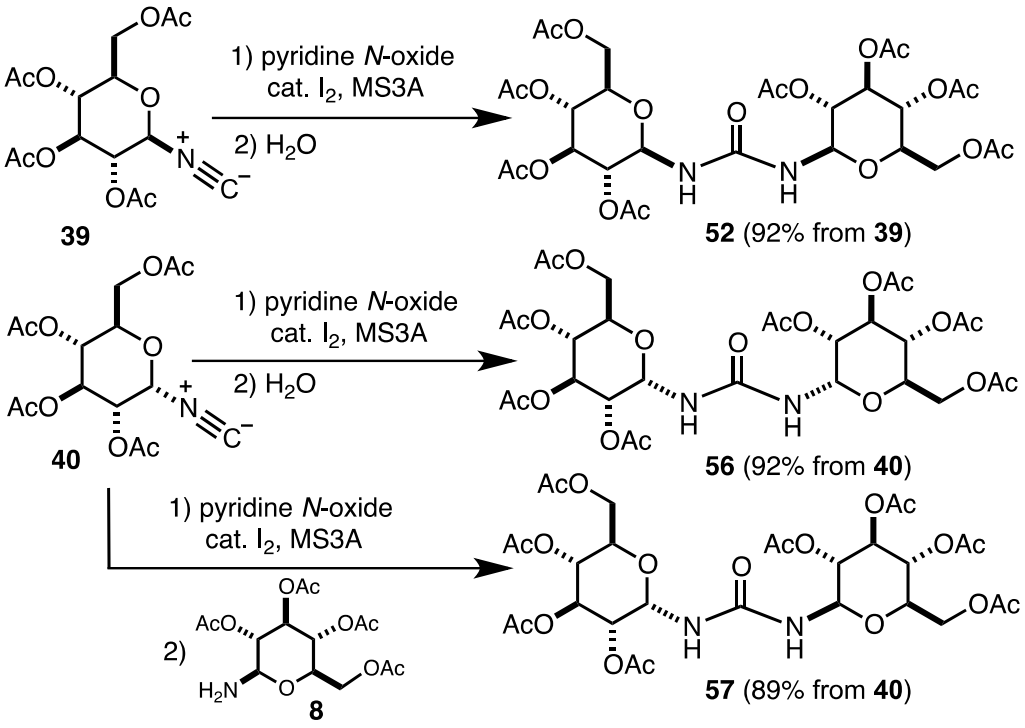
the product by chromatography yielded α-GP urea **55** in 92% yield. To the best of my knowledge, this is the first example of the synthesis of α-GP isocyanate and urea.



Scheme 18. Synthesis of α-Glucopyranosyl Isocyanide and Its Transformation to α-Glucopyranosyl Isocyanate and Urea

3-3. Synthesis of Three Isomers of Urea-Tethered Trehalose Mimics

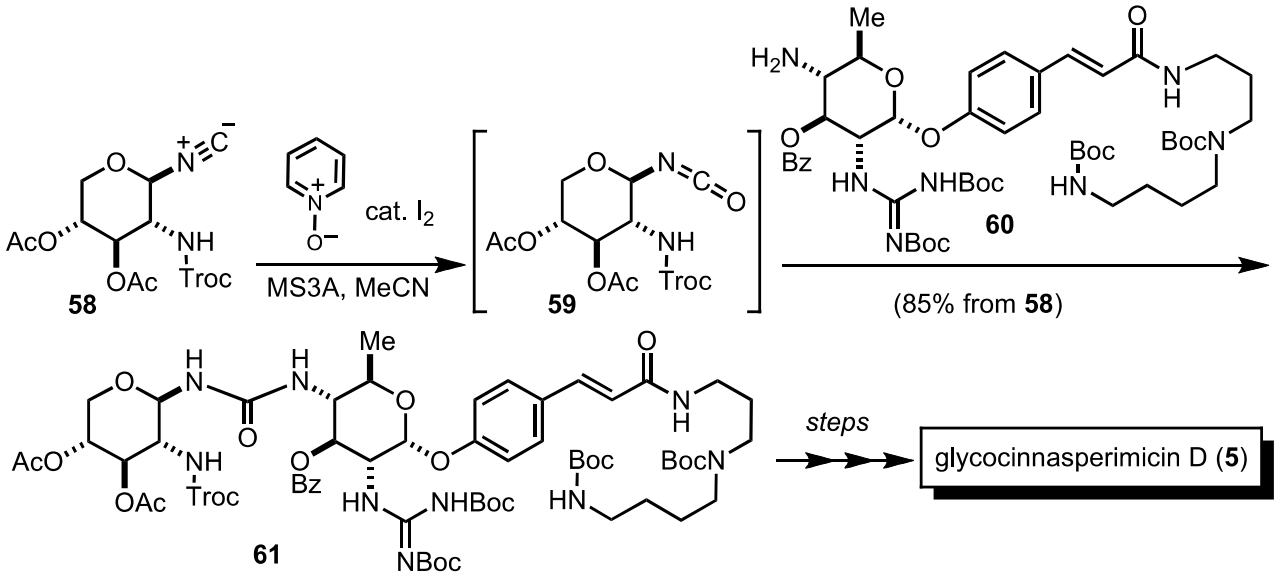
We were interested in the unique structure of the by-product, *N,N'*-di-β,β-D-GP urea **52** (Scheme 17), in which two glucose units join at the anomeric positions through a urea moiety with β-stereochemistry. Although this bis-GP urea was known to be a product of acid-catalyzed condensation reaction of D-glucose with urea,[3d] its stereoisomers have never been reported. Armed with the isocyanide method for the stereospecific synthesis of α- and β-GP isocyanate and respective urea, we sought to synthesize all stereoisomers of the bis-GP urea (Scheme 19).[17] Oxidation of β-GP isocyanide **39** was carried out employing the procedure described in Scheme 17. After checking the disappearance of starting β-GP isocyanide **39** by using TLC, water was added to the reaction mixture leading to the formation of **52** in 92% yield. Following the same sequence of reactions as before, the α-GP isocyanide **40** was converted to *N,N'*-α,α-GP urea **56** in 92% yield. This compound mimics the naturally occurring disaccharide α,α-trehalose in which two glucose units are joined through oxygen with α-stereochemistry. Finally, oxidation of α-GP isocyanide **40** followed by ensuing treatment of the reaction mixture with β-amine **8** afforded *N,N'*-di-α,β-GP urea **57** in 89% yield. Thus, the isocyanide method we developed enabled successful stereospecific synthesis of the three isomers of *N,N'*-di-GP ureas.



Scheme 19. Stereospecific Syntheses of All Isomers of *N,N'*-di-Glucopyranosyl Ureas

3-4. Isocyanide Method in the Total Synthesis of Glycocinnasperimicin D

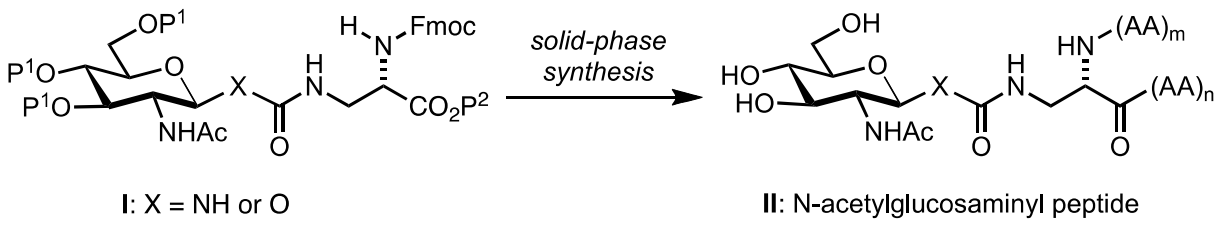
In the final stage of the total synthesis of glycocinnasperimicin D, we showcased the isocyanide method to construct the urea glycoside in the presence of a variety of nitrogen-containing functional groups in aminosugars **58** and **60** (Scheme 20).[38] Specifically, oxidation of the isocyanide **58** with pyridine *N*-oxide in the presence of molecular sieves 3A and a catalytic amount of iodine in acetonitrile generated the isocyanate **59**, which was subsequently treated with aminosugar **60**. To our delight, this process gave rise to the desired coupling product **61** in high yield (85%). Introduction of the urea moiety on left-side aminosugar in **61** and global deprotection furnished the long-awaited glycocinnasperimicin D (**5**). Thus, utilization of the isocyanide method bore fruit at the crucial coupling event in this first total synthesis of glycocinnasperimicin D (**5**). Nishiyama wrote his doctorial dissertation based upon this total synthesis of glycocinnasperimicin D.



Scheme 20. Final Stage for the Total Synthesis of Glycocinnasperimicin D

3-5. Synthesis of *N*-Acetyl-D-glucosamine Amino Acid Conjugate

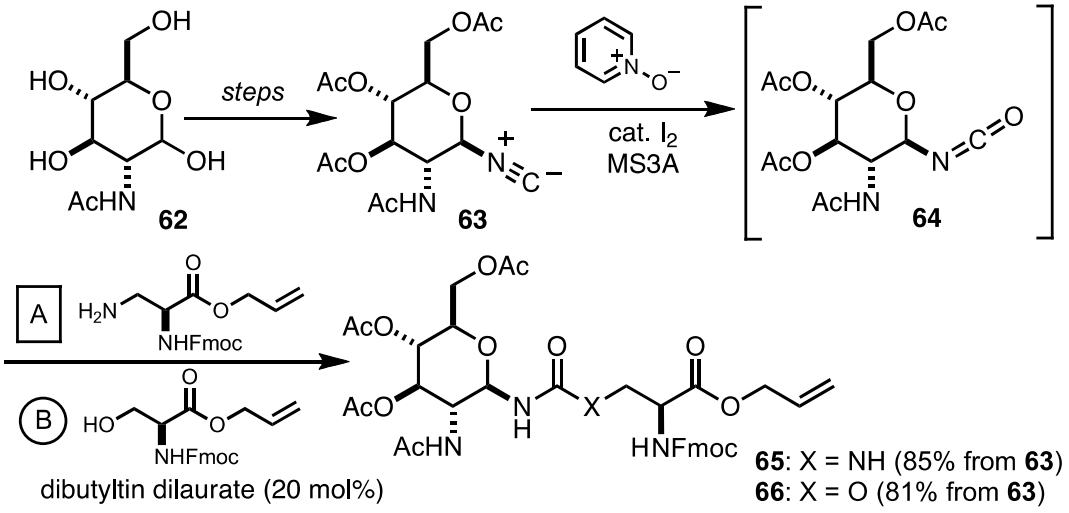
The importance of the carbohydrates linked to peptide backbones of proteins have become the focus of bioorganic and/or medicinal research work due to their involvement in diverse biochemical processes such as cellular recognition and adhesion.[39] In this research area, the design and synthesis of glycopeptide mimetics continues to attract much attention in order to supply homogeneous, stable and readily accessible glycopeptide analogues for biological studies and therapeutic applications.[40] In studies of glycopeptide mimetics, natural covalent bonds between carbohydrates and peptides have been replaced by non-native linkages. Our research endeavors to develop the synthesis of glycopeptide mimetics, in which *O*- and *N*-glycosyl linkages are replaced by urea- or carbamate-glycosyl bonds, led to a plan for the solid-phase synthesis of *N*-acetyl-D-glucosaminyl neoglycopeptide **II** based on the Fmoc-strategy (Scheme 21).[41] In a prelude to studies of the synthesis of neoglycopeptide, we examined the preparation of urea- and carbamate-tethered glycosyl amino acid conjugates **I**.



Scheme 21. A Plan for the Solid-Phase Synthesis of *N*-Acetyl-D-glucosaminyl Neoglycopeptide

N-Acetyl-D-glucosamine isocyanide **63** was prepared starting with commercially available *N*-acetyl-D-glucosamine **62** (Scheme 22). Oxidation of *N*-acetyl-D-glucosamine isocyanide **63** generated

the corresponding isocyanate **64**, which subsequently reacted with α,β-diamino acid **A** to form the urea-tethered, Fmoc-protected, *N*-acetyl-D-glucosamine amino acid conjugate **65** in 85% yield. Although reaction of *N*-acetyl-D-glucosamine isocyanate **64** with serine derivative **B** was sluggish and low-yielding, addition of 20 mol% dibutyltin dilaurate as a promoter successfully improved this coupling process to furnish **66** in 81% yield.

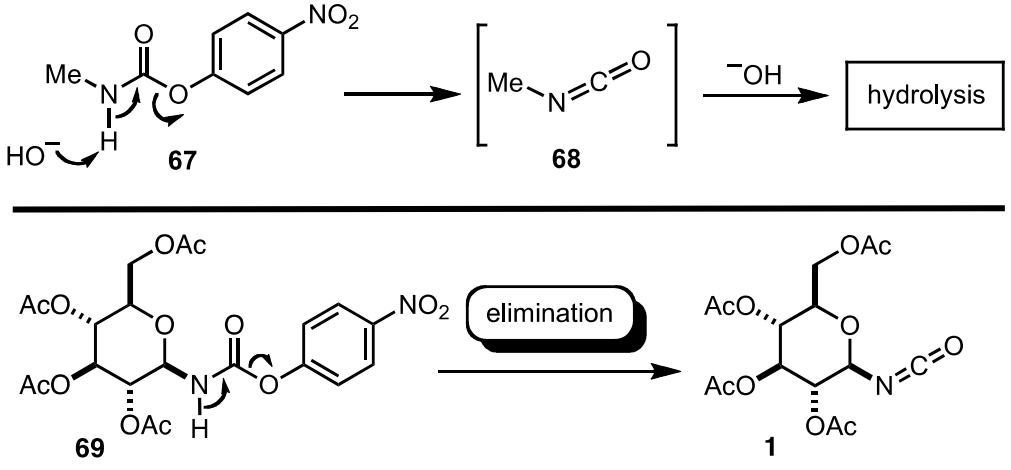


Scheme 22. Synthesis of Fmoc-Protected *N*-Acetyl-D-glucosamine Amino Acid Conjugate

4. CARBAMATE METHOD FOR THE PREPARATION OF GLUCOPYRANOSYL ISOCYANATES

4-1. Synthesis of Glucopyranosyl Isocyanates by Elimination Reaction of Carbamate

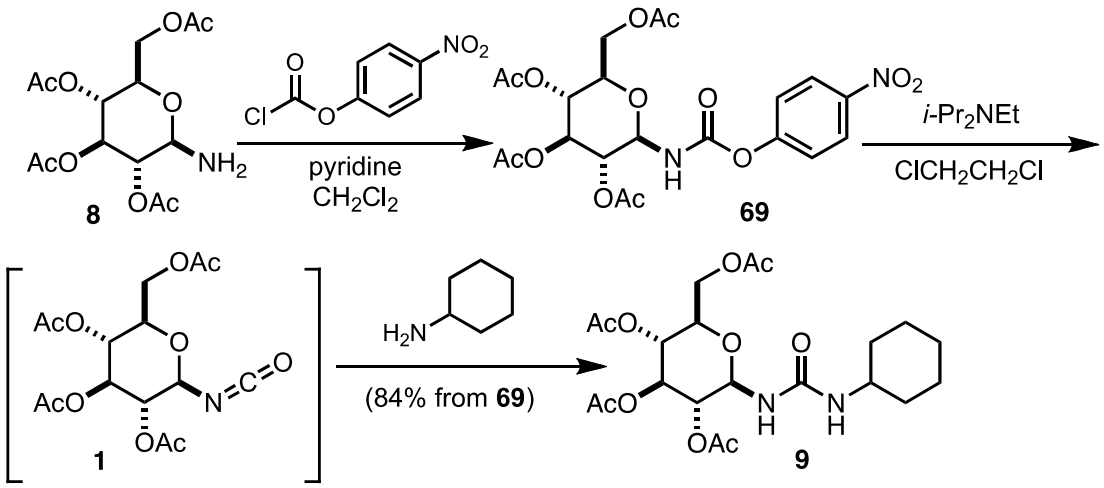
The third method developed for the synthesis of GP isocyanates was inspired by the mechanism of the hydrolysis reaction of carbamates (Scheme 23). The kinetic investigation of the alkaline hydrolysis of



Scheme 23. Synthetic Plan for Glucopyranosyl Isocyanates Inspired by Elimination-Addition Mechanism

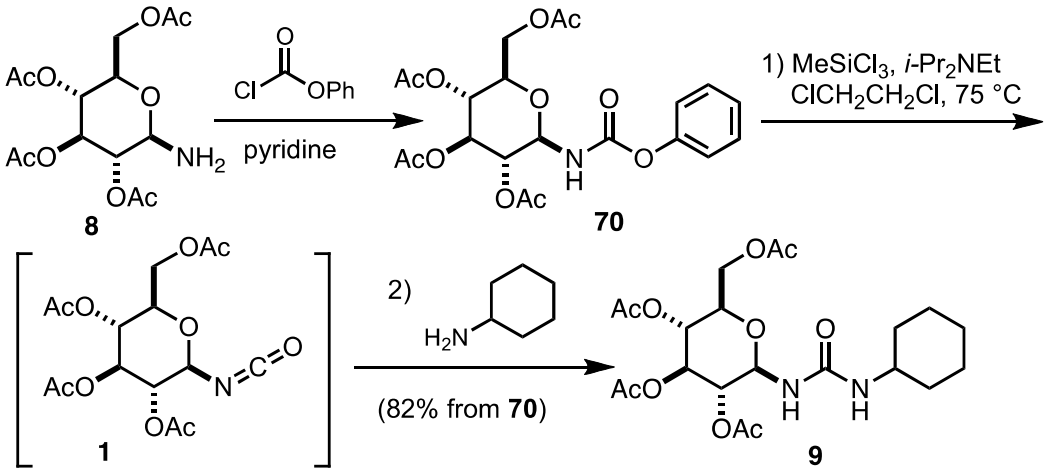
p-nitrophenyl *N*-methylcarbamate (**67**) revealed the elimination-addition mechanism in which methyl isocyanate (**68**) is postulated as an intermediate.[42] With this mechanistic insight in mind, we explored a new synthetic method for the preparation of β-GP isocyanate **1** that involves elimination reaction of β-GP carbamate **69** (carbamate method).[43]

In this effort, we prepared *p*-nitrophenyl β-GP carbamate **69** by the reaction of β-GP amine **8** with *p*-nitrophenyl chloroformate and pyridine to furnish **69** as pale yellow crystals (Scheme 24). As expected, base-catalyzed elimination of *p*-nitrophenyl β-GP carbamate **69** occurred quite readily upon treatment with diisopropylethylamine in 1,2-dichloroethane at room temperature. This process formed a yellow solution of β-GP isocyanate **1**, which was subsequently treated with cyclohexylamine to yield β-GP urea **9** in 84% yield in a one-pot process. Although we were delighted with these results, we found a problem associated with storage of **69**, because it gradually decomposed even in a freezer. Moreover, purification of **69** by silica-gel chromatography led to considerable decrease in its recovery. As a result, we next explored an alternative elimination reaction using more stable GP carbamates.



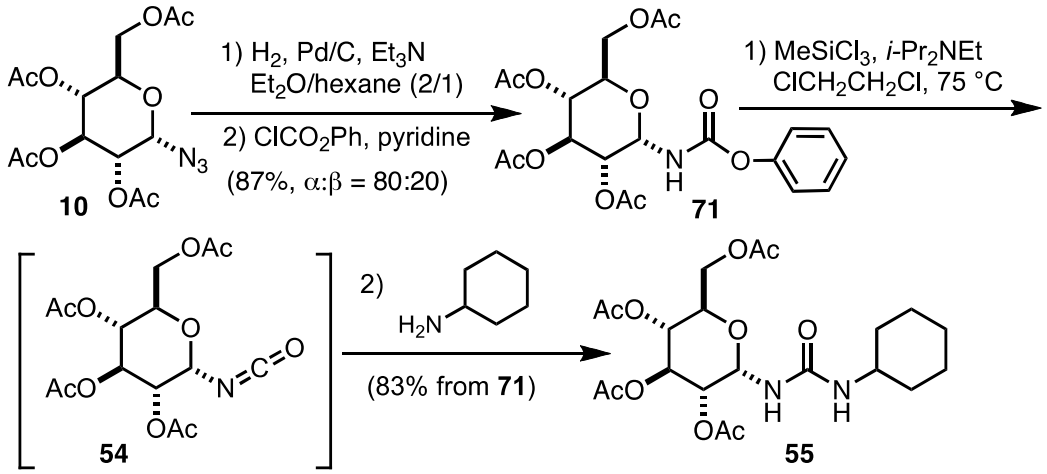
Scheme 24. Carbamate Method for the Synthesis of β-Glucopyranosyl Isocyanate and Urea

After some experimentation, we have developed a method, which employs silyl-promoted elimination reaction of phenyl carbamates (Scheme 25).[44] Specifically, phenyl β-GP carbamate **70**, prepared by treatment of β-GP amine **8** with phenyl chloroformate, was found to undergo smooth elimination (1.5 equiv of $MeSiCl_3$, 4.0–5.0 equiv of *i*-Pr_2NEt, 1,2-dichloroethane, 75 °C, 5 hours) to form a solution of β-GP isocyanate **1**. Subsequent treatment of the reaction mixture with cyclohexylamine (2.0 equiv) produced β-GP urea **9** in 82% yield.



Scheme 25. Silyl-Promoted Elimination Reaction of Phenyl Carbamate to Generate Glucopyranosyl Isocyanate

Encouraged by this result, α-phenyl carbamate **71** was also prepared from α-GP azide **10** (Scheme 26). Catalytic hydrogenation of **10** followed by immediate treatment of the reaction mixture with phenyl chloroformate and pyridine generated a 4:1 anomeric mixture of phenyl carbamates with the desired α-isomer **71** predominating in 87% yield. Although these anomers could be separated by careful silica-gel chromatography, α-GP carbamate **71** was much more conveniently separated and purified by recrystallization. Using a procedure similar to that given in Scheme 25, silyl-promoted elimination of α-GP carbamate **71** produced the corresponding α-GP urea **55** in 83% yield. Examination of the crude product mixture by ^{1}H NMR analysis confirmed that the β-isomer was not formed, which clearly showed that elimination of α-GP carbamate **71** generated α-GP isocyanate **54** stereospecifically.

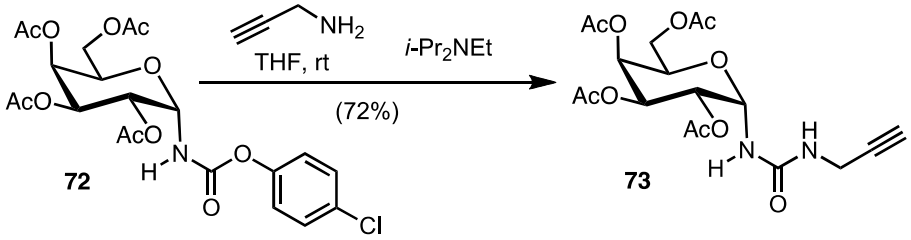


Scheme 26. Carbamate Method for the Synthesis of α-Glucopyranosyl Isocyanate and Urea

It should be noted that while the isocyanide method gave slightly better yields (Scheme 18), the route employing the carbamate method enables ready production of both GP carbamates **70** and **71** from the respective GP azides in two steps using commercially available reagents. Moreover, a practical merit of the carbamate method concerns the fact that α-GP carbamate **71** can be easily separated and purified due to its high crystallinity.

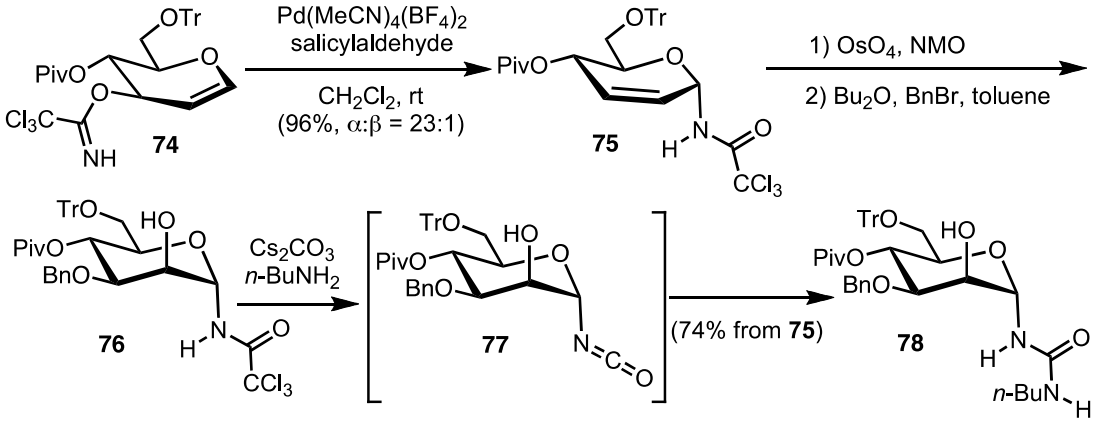
4-2. Further Development of the Carbamate Method Reported by Liskamp and Nguyen

Liskamp reported an improved method for the synthesis of ureido glycosides using the stable 4-chlorophenyl carbamate **72** (Scheme 27).[45] In this case, a THF solution of carbamate **72** and propargyl amine was treated with diisopropylethylamine, leading to the elimination of chlorophenol followed by addition of propargyl amine to produce **73** in 72% yield. This simple experimental procedure demonstrated that the 4-chlorophenyl glycosyl carbamate synthon serves as a masked glycosyl isocyanate.



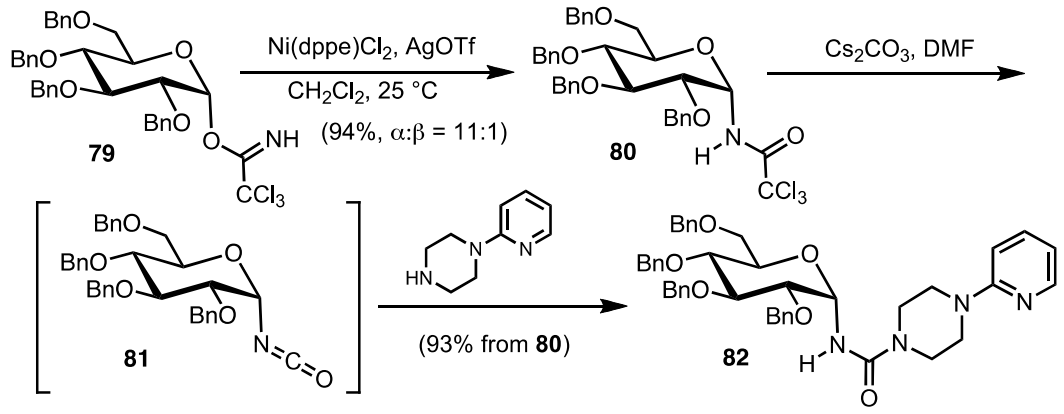
Scheme 27. Synthesis of α-Galactopyranosyl Urea Using 4-Chlorophenyl Carbamate

Nguyen reported a unique approach for the stereoselective synthesis of α- and β-mannopyranosyl ureas in which elimination of trichloroacetamide rather than carbamate was used for generation of mannopyranosyl isocyanate (Scheme 28).[46] In this process, glycal trichloroacetimidate **74** underwent cationic Pd(II)-catalyzed glycal imidate rearrangement via a stepwise ionization-recombination pathway to afford α-trichloroacetamide **75**. Osmium tetraoxide-catalyzed dihydroxylation of **75** followed by selective benzylation of the resulting *cis*-diol formed the *N*-mannopyranosyl trichloroacetamide **76**. Removal of the trichloroacetamide proton in **76** led to elimination of trichloromethyl anion to generate an isocyanate **77** in situ, which subsequently reacted with *n*-butylamine to form α-mannopyranosyl urea **78** in 74% yield. The stereochemical integrity at the anomeric carbon remains in tact during the elimination-addition steps. The strategy to generate glycosyl isocyanate by using elimination reaction of trichloroacetamide glycoside is an interesting extension of the carbamate method for the synthesis of glycosyl isocyanate.



Scheme 28. Synthesis of α-Mannopyranosyl Urea via Elimination Reaction of Trichloroacetamide

Nguyen developed an alternative method for the synthesis of α-GP ureas starting from α-GP trichloroacetimidates (Scheme 29).[47] A cationic nickel catalyst promoted the ionization and recombination of trichloroacetimidate **79**, leading to the selective formation of α-GP trichloroacetamide **80**. Elimination of **80** followed by trapping the in situ generated α-GP isocyanate **81** with pyridylpiperazine provided α-GP urea **82** in 93% yield.



Scheme 29. Synthesis of α-Glucopyranosyl Urea Using Nickel-Catalyzed Rearrangement of α-Glucopyranosyl Trichloroacetimidate

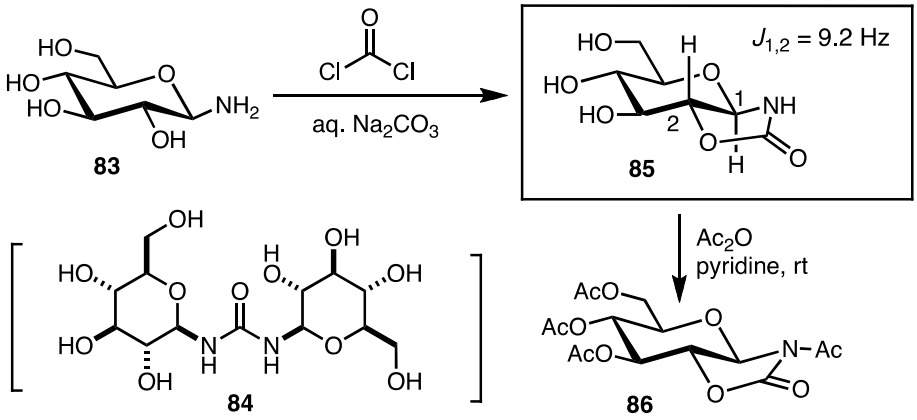
5. STEYERMARK'S OXAZOLIDINONE

5-1. Historical Background of Steyermark's Oxazolidinone

While our research endeavors established that GP isocyanate is a good starting material for the synthesis of glycoconjugates, hydroxy groups in GP isocyanate are protected as acetates, and its reaction should be carried out in organic solvents under strictly anhydrous conditions to avoid hydrolysis of isocyanate function. Consideration of these issues led to the imaginative and challenging question: 'Does a

synthetic equivalent of GP isocyanate exist, which tolerates free hydroxy groups and glycoconjugation reactions in aqueous media'. The answer to this intriguing question is found in the Steyermark's oxazolidinone.[48]

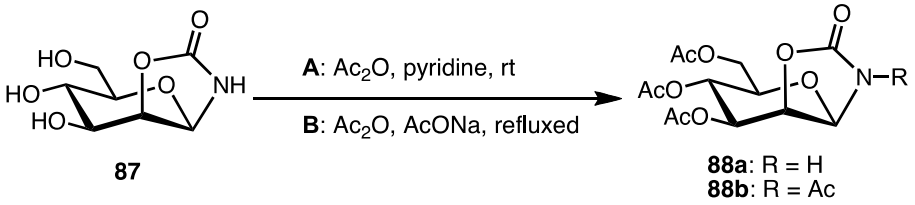
In 1962, Steyermark reported the reaction of β-GP amine **83** with phosgene, which he expected to produce the known *N,N'*-di-β,β-D-GP urea **84** (Scheme 30).[49] Contrary to his expectation, the actual product generated in this process was the cyclic carbamate **85** in low yields ranging from 6 to 30%. The pyranose structure of **85** was proposed through periodic acid oxidation and transformation of the product to the tetraacetate by treatment with acetic anhydride and pyridine at room temperature. The stereochemistry at the anomeric position in **85** was erroneously assigned as α-configuration by analyzing optical rotation values. In 1985, an improved synthesis of **85** using the reaction of β-GP phosphinimine with carbon dioxide was reported by Pinter, who also demonstrated the correct stereochemistry at the anomeric position.[50] Specifically, the large coupling constant between H-1 and H-2 in the ^{1}H NMR of **85** ($J_{1,2}$ = 9.2 Hz) unambiguously shows that the oxazolidinone moiety is fused to the pyranose ring in a bis-equatorial *trans*-manner.



Scheme 30. Unexpected Reaction of Glucopyranosyl Amine with Phosgene

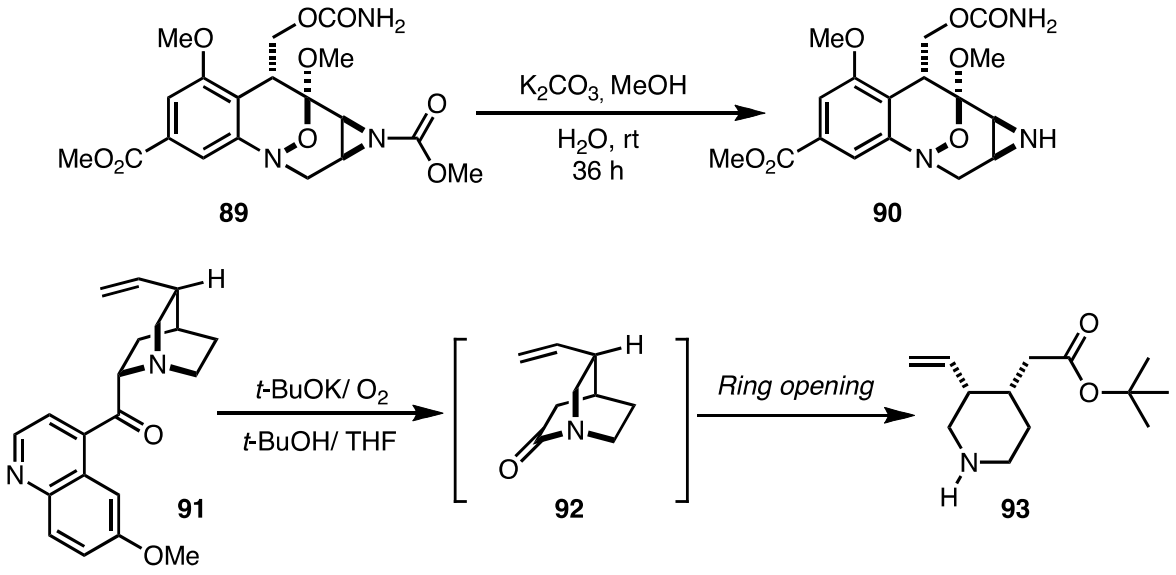
5-2. Analysis of the Anomalous Reactivity of *trans*-Fused Oxazolidinone

I was attracted to the anomalous reactivity of Steyermark's oxazolidinone **85** in that *N*-acetylation occurred under mild conditions (Ac_2O, pyridine, room temperature, usually employed for *O*-acetylation). Since nitrogen in oxazolidinone is conjugated with a carbonyl group, *N*-acetylation should not take place under such mild conditions. In fact, the reactivity of nitrogen in the *trans*-fused Steyermark's oxazolidinone **85** is in sharp contrast to that of *cis*-fused oxazolidinone **87** derived from mannose (Scheme 31).[51] Treatment of mannopyranosyl oxazolidinone **87** with acetic anhydride and pyridine at room temperature (conditions **A**) led to *O*-selective acetylation to afford triacetate **88a**. In contrast, *N*-acetylation of **87** occurred only under more forcing conditions using acetic anhydride and sodium acetate at reflux (conditions **B**) to produce tetraacetate **88b**.



Scheme 31. Acetylation of *cis*-Fused Mannopyranosyl Oxazolidinone

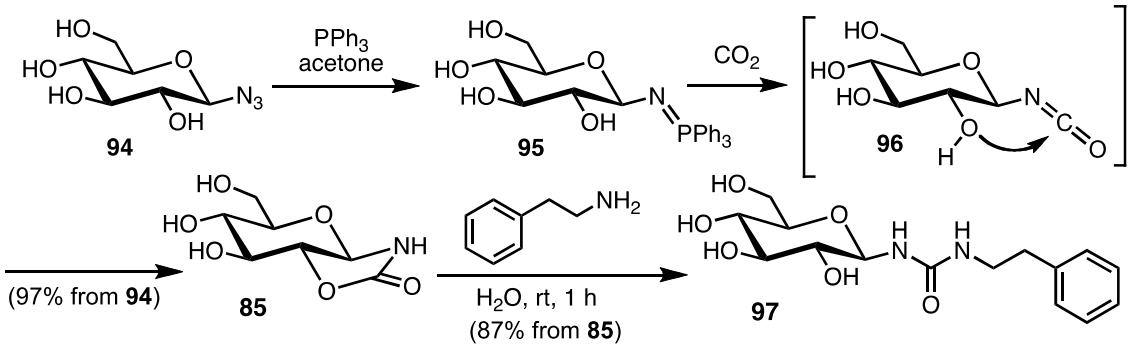
The anomalous reactivity of Steyermark's oxazolidinone **85** found in *N*-acetylation clearly indicated that the twisted structure of the bis-equatorial *trans*-fused oxazolidinone prevented delocalization of the lone pair electrons on nitrogen into the carbonyl group. It was well known that carbonyl groups attached to nitrogen have increased kinetic reactivity towards nucleophilic addition/hydrolysis when delocalization of the nitrogen lone pair electrons into the carbonyl group is disturbed. For example, methyl carbamate **89** underwent smooth hydrolysis without affecting the methyl ester moiety to afford **90** (Scheme 32).[52] This facile hydrolysis reaction is a likely consequence of the fact that delocalization of the nitrogen lone pair would increase angle strain in the aziridine ring. On the other hand, in the degradation studies of quininone **91**, Doering found that the amide carbonyl in **92** behaves as an acylating center that reacts with potassium *tert*-butoxide to form *tert*-butyl ester **93**.[53] In this case, the bicyclic structure in **92** prevented overlap of the lone pair electrons on the bridgehead nitrogen with the carbonyl group. Based on these precedents, we anticipated that the carbonyl group in the Steyermark's oxazolidinone **85** should exhibit increased kinetic reactivity towards nucleophilic attack, and this is indeed found to be the case.



Scheme 32. Unusual Reactivity of Twisted Carbonyl Group Attached to Nitrogen

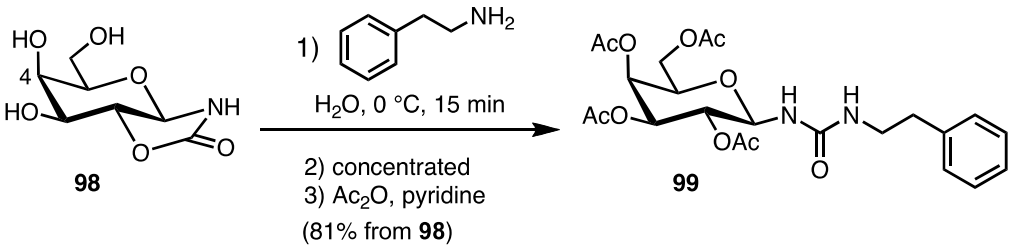
5-3. Syntheses of Glycoconjugates and Urea-Tethered Pseudooligosaccharides in Aqueous Media

We have unraveled the unusual reactivity of carbonyl group in Steyermark's GP oxazolidinone **85** (Scheme 33). Steyermark's GP oxazolidinone **85** was prepared using the modified procedures reported by Pinter. Staudinger reaction of β-GP azide **94** with triphenylphosphine in acetone afforded phosphinimine **95**, which was subsequently treated with carbon dioxide in a one-pot process. A plausible mechanism for formation of oxazolidinone **85** involves aza-Wittig reaction of **95** with carbon dioxide to form β-GP isocyanate **96**, which spontaneously cyclized by intramolecular attack of the C-2 hydroxy group on the neighboring isocyanate group, resulting in the cyclized product **85**. Indeed, the isocyanate moiety is confined to the *trans*-fused oxazolidinone ring. While hydrolysis of Steyermark's oxazolidinone **85** occurred even in neutral media (about 60% of **85** was hydrolyzed in D_2O at 40 °C after 24 hours, monitored by ^1H NMR), it underwent smooth ring-opening reaction with 2-phenylethylamine in water (room temperature, 1 hour) to furnish β-GP urea **97** in 87% yield without noticeable side-reactions such as hydrolysis. These experiments showed that Steyermark's GP oxazolidinone **85** has potential use as a water-soluble synthetic equivalent of Fischer's GP isocyanate **1**.



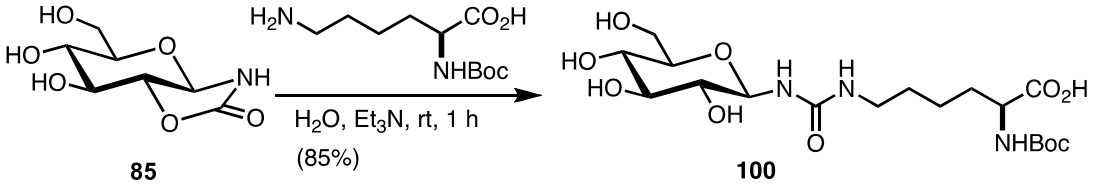
Scheme 33. Urea Glucosylation of Steyermark's Glucopyranosyl Oxazolidinone in Water

We also examined the reaction of galactose-type oxazolidinone **98** with amines in water (Scheme 34).[54] Ring opening reaction of oxazolidinone **98** with 2-phenylethylamine proceeded more rapidly (0 °C within 15 minutes) than that of Steyermark's GP oxazolidinone **85** to produce β-galactopyranosyl urea **99** in 81% yield after acetylation and purification. The more highly reactive nature of galactose-type oxazolidinone **98** compared with that of the glucose-type **85** may be a result of the axial orientation of hydroxy group at C-4, which destabilizes the ground state structure of **98**.



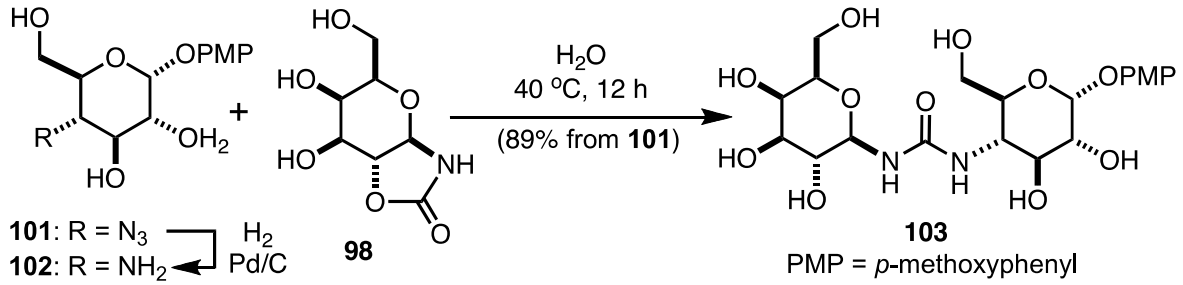
Scheme 34. Urea Glycosylation of *trans*-Fused Oxazolidinone Derived from Galactose

In order to disclose the potential of Steyermark's GP oxazolidinone **85** as a synthon for the synthesis of glycoconjugates in water, we explored the synthesis of a urea-tethered glucosyl amino acid conjugate (Scheme 35). Reaction of **85** with the ε-amino group of lysine in the presence of triethylamine proceeded at room temperature within 1 hour to produce the urea-tethered glucosyl lysine conjugate **100** in 85% yield.



Scheme 35. Anchoring a Carbohydrate Moiety onto an Amino Acid Using Steyermark's Oxazolidinone

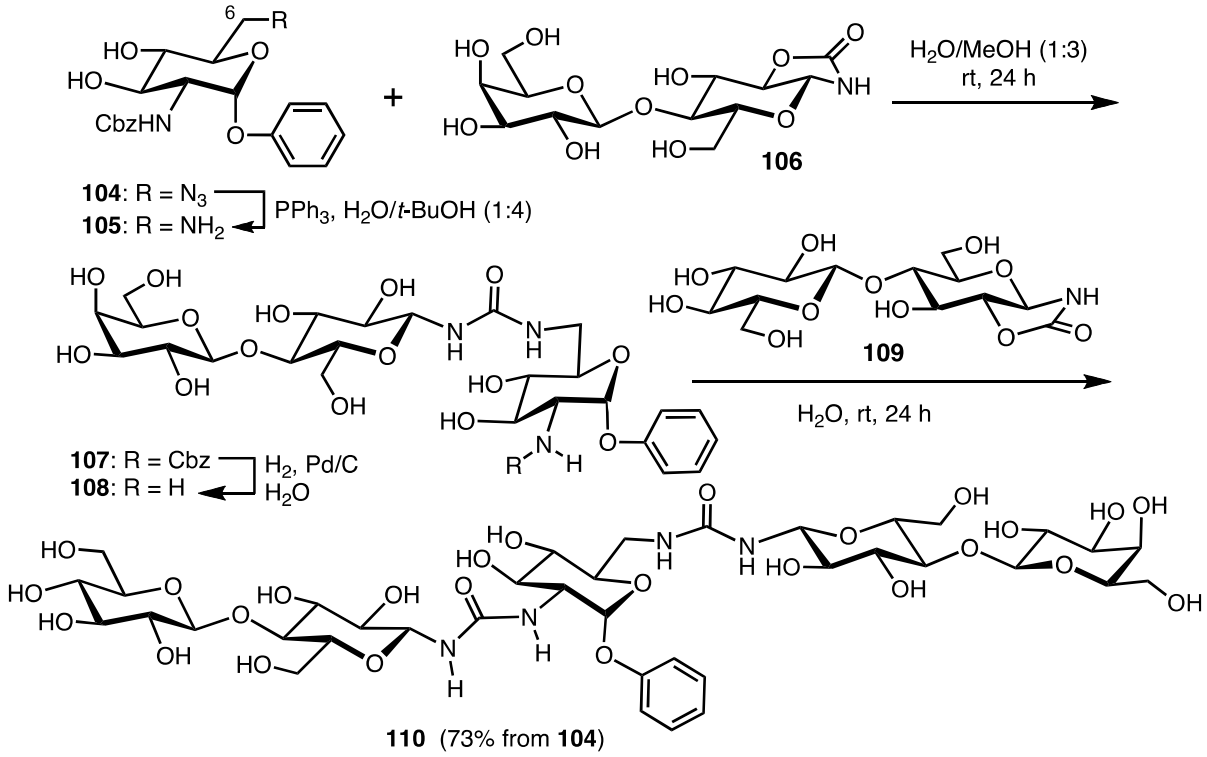
Further development of Steyermark-type GP oxazolidinone as a water-soluble synthetic equivalent of GP isocyanate was realized by its application to the synthesis of a urea-tethered lactose analogue (Scheme 36). Reaction of 4-aminohexopyranose **102**, prepared by catalytic hydrogenation of azide **101**, with two equivalents of galactose-type oxazolidinone **98** in water proceeded at 40 °C for 12 hours to furnish the urea-linked lactose analogue **103** in 89% yield.



Scheme 36. Synthesis of Urea-Linked Lactose Analogue in Water

We further expanded the utility of Steyermark-type GP oxazolidinone in the synthesis of a urea-tethered pentasaccharide (Scheme 37). A core segment, phenyl 2,6-diaminoglycoside **104** having two ligation

sites for the urea-glycosylation, was prepared from D-glucosamine hydrochloride. Selective activation of the C-6 azide moiety in **104** was accomplished by Staudinger reaction followed by hydrolysis of the formed intermediate phosphinimine. The amine **105** produced in this process was treated with lactosyl oxazolidinone **106** at room temperature in aqueous media (H_2O/MeOH, 1:3) for 24 hours to produce urea-tethered trisaccharide **107**. The second activation was carried out by hydrogenolysis of the Cbz-group in **107** to afford the amine **108**, which was subsequently treated with cellobiosyl oxazolidinone **109** in water. The reaction mixture was stirred at room temperature for 24 hours, and then subjected to the reversed phase column chromatography to furnish urea-linked pentasaccharide **110** in 73% overall yield starting from **104**. While most ^{1}H NMR signals in the spectrum of **110** are overlapped, ^{13}C NMR and FAB mass spectra confirmed the structure of this novel urea-tethered pentasaccharide. Specifically, the ^{13}C NMR spectrum of **110** displayed two urea-carbonyl carbons (δ 159.8 and 160.2 ppm), four aromatic carbons (δ 118.2, 124.0, 130.7 and 156.7 ppm) and thirty carbons corresponding to the five hexopyranoses. Among ^{13}C NMR signals associated with the hexose portions, the two peaks at δ 81.5 and 81.6 ppm correspond to two anomeric carbons linked to ureido nitrogen, which are consistent with the assignment of β-stereochemistry.[17] The signal at δ 97.6 ppm is assigned to an anomeric carbon of the the phenyl glycoside and the peaks at δ 103.2 and 103.6 ppm are attributed to the anomeric carbons of the lactose and cellobiose moieties.



Scheme 37. Synthesis of Urea-Tethered Pentasaccharide in Aqueous Media

6. ANOMERIC EFFECT OF THE NITROGEN ATOM IN THE ISOCYANIDE

6-1. Anomeric Effect of *N*-Glycosides

The anomeric effect defined the preference for the axial orientation of electronegative substituents at C-1 of a pyranose ring, which is in marked contrast to expectations based on the sterically driven preference for equatorial cyclohexane conformers.[55] Elements in the first row of the periodic table display the anomeric effect, the magnitude of which diminishes with decreasing electronegativity of the element (F>O>N>C).[56] In the case of nitrogen, the axial preference depends on the substituents at the nitrogen center. Paulsen examined the conformational equilibrium for *N*-substituted *N*-pentopyranosylamine derivatives by ^{1}H NMR spectroscopy and showed that the order of axial preference is as follows: N=PPh_3>OAc>N_3>$NHCOCF_3$>NHCOAr> NH_2 = NHAc.[57] The anomeric effect is largest for more electronegative sp and sp^2-hybridized nitrogen groups, while substituents such as NH_2 and NHAc show the usual sterically driven preference for equatorial dispositions.

6-2. Anomalous ^{1}H NMR Coupling Constants of *N*-Glycosides Observed in Synthetic Studies of Glycocinnasperimicin D

In the course of synthetic studies of glycocinnasperimicin D, I was surprised to observe an anomalous change in ^{1}H NMR coupling constants in the left-hand amino sugar key intermediates (Figure 7).[58] The H-1 resonance of **58** appears at a low field (δ = 5.50 ppm) as a doublet ($J_{1,2}$ = 5.5 Hz) indicating that H-1 and H-2 are gauche-disposed. In contrast, transformation of **58** to urea glycoside **111** results in the large change in the coupling constant ($J_{1,2}$ = 10.0 Hz), which is in accord with the trans-diaxial arrangement of H-1 and H-2. These observations suggested that an unusual conformational difference exists as a consequence of the change in substituents at the anomeric position. In particular, isocyanide group in **58** most likely prefers an axial orientation, suggesting an anomeric effect of the isocyanide group.

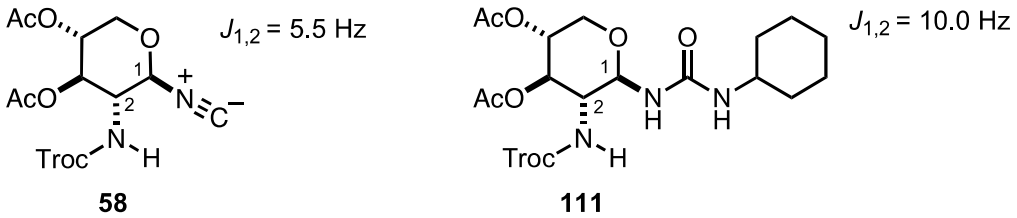
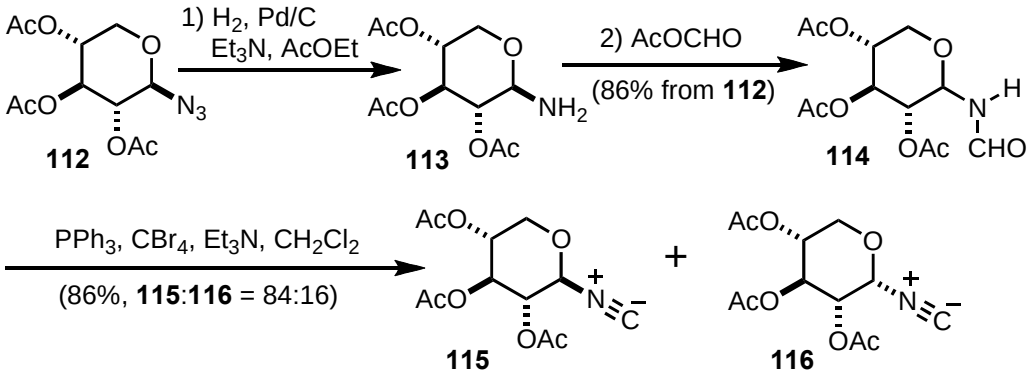


Figure 7. Revelation of Anomeric Effect of Isocyanide Group

6-3. Securing the Anomeric Effect of an Isocyanide Group

In 2004, I left Nagoya University and emigrated from Tōkai region in central Honshū to the island of Shikoku to join the Faculty of Science at Kochi University. As a starting research project at Kochi

University, I planned to develop the synthesis of glycoconjugates using pentose isocyanates. Our initial synthetic efforts focused on the synthesis of β-xylopyranosyl isocyanide **115** starting from β-azide **112** (Scheme 38). During scale-up of this synthesis, we found that the α-anomer **116** was also formed as a minor product, presumably arising by isomerization of β-xylopyranosyl amine **113** during its preparation and/or formylation steps. To our delight, this fortuitous observation led to isolation of α-isocyanide **116** as a crystalline compound. Contrary to the initial plan, we diverted the research program to explore the anomeric effect of the isocyanide group using the anomeric pair of xylopyranosyl isocyanides **115** and **116** by carrying out conformational analysis using ^{1}H NMR spectroscopy.



Scheme 38. Unexpected Isolation of an Anomeric Pair of Xylopyranosyl Isocyanides

The 400 MHz ^{1}H NMR spectrum of each of the xylopyranosyl isocyanides, **116** and **115**, measured in $CDCl_3$ is shown in Figure 8. The ^{1}H NMR data of the α-isocyanide **116** are fully consistent with the

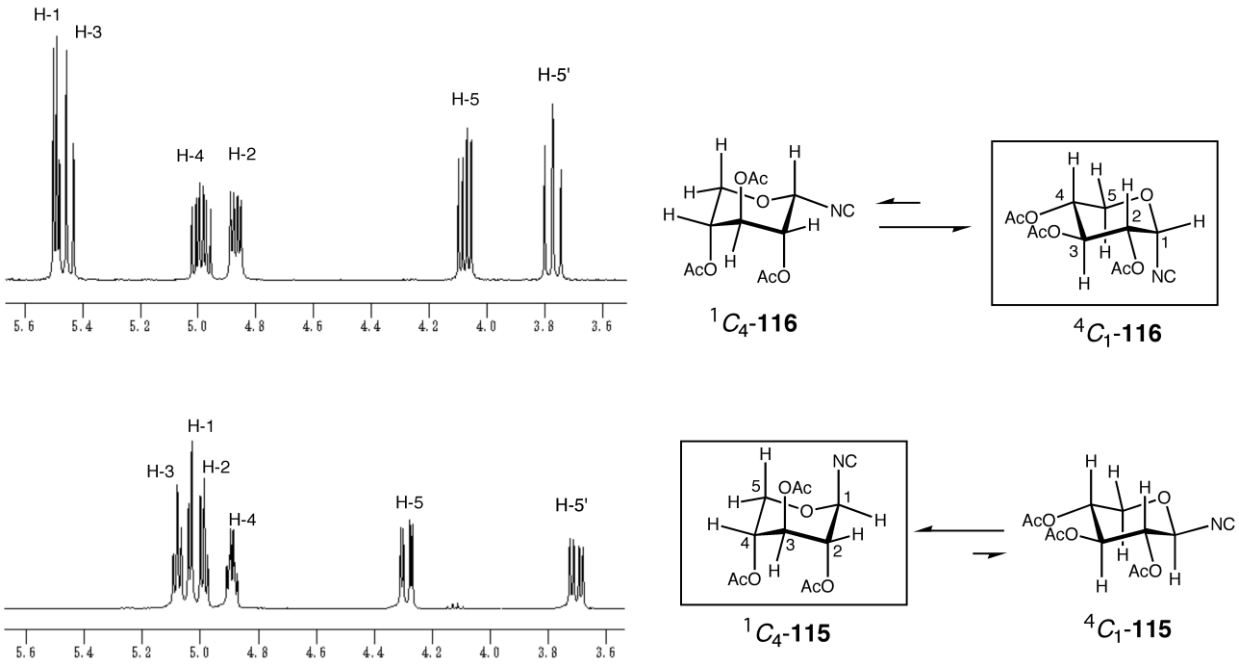
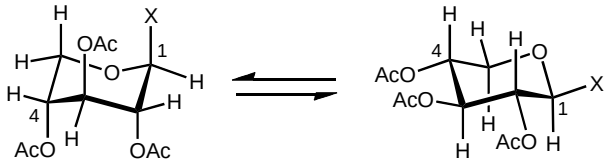


Figure 8. ^{1}H NMR Spectra of Xylopyranosyl Isocyanides **116** and **115** in $CDCl_3$

assignment of the $^4C_1$ conformation. In contrast, β-isocyanide **115** has a remarkably different ^{1}H NMR spectrum from that of the α-anomer **116**. The isocyanide group at C-1 in **115** appears to be axially oriented leading to adopt the $^1C_4$ conformation preferentially. These observations, coupled with the results of X-ray crystallographic analysis, established that the isocyanide group displays an anomeric effect.[59]

Using the observed time-averaged values of $J_{4,5}$ and $J_{4,5'}$, we calculated the conformational populations of the $^1C_4$ and $^4C_1$ conformers of the xylopyranosyl isocyanides to be $K = {}^4C_1/{}^1C_4 = 6.6$ for α-isocyanide **116** and 0.58 for β-anomer **115**. In order to estimate the magnitude of the anomeric effect of the isocyanide group, we collected and compared the equilibrium constant ($K = {}^4C_1/{}^1C_4$) of each tri-*O*-acetyl-β-D-xylopyranosyl chloride **117**,[60] acetate **118**[61] and azide **112**[57] with that of isocyanide **115** (Table 2). The data showed that the order of axial preference in β-xylopyranosyl derivatives as follows: –Cl > –NC > –OAc > –N_3. Our studies provided confirmation of the first example of the anomeric effect of the nitrogen in an isocyanide.

Table 2. Equilibrium Constants ($K = {}^4C_1/{}^1C_4$) of Tri-*O*-acetyl-β-D-xylopyranosyl Derivatives



$^1C_4$-conformer $^4C_1$-conformer

	117 (X = Cl) [a]	**118** (X = OAc)[b]	**112** (X = N_3)[c]	**115** (X = NC)
$K = {}^4C_1/{}^1C_4$	0.26	2.6	4.0	0.58

[a] Calculated by ^{1}H NMR analysis measured in $CDCl_3$ at 31 °C. [b] Calculated by ^{1}H NMR analysis measured in acetone-d_6 at 31 °C. [c] Calculated by ^{1}H NMR analysis measured in $CDCl_3$.

7. CONCLUSIONS

When I accepted a kind invitation from the Editor of HETEROCYCLES, the late Professor Keiichiro Fukumoto, to write a review focusing on our research studies, I originally thought to use the title 'Synthesis of Glycosyl Ureas'. However, during preparation of the manuscript, I noticed Nguyen's review 'Recent developments in glycosyl urea synthesis' published in 2014.[62] In order to avoid overlapping this article, I reconstructed the manuscript emphasizing on glycopyranosyl isocyanates and isocyanides. But, the question is why did I choose 'isocyanates and isocyanides'. To address this question, I would like to trace my scientific career briefly.

In 1979, an undergraduate student (Y. I.) joined the Laboratory of Organic Chemistry (LCO) in the Faculty of Agricultural Sciences at Nagoya University. LCO is one of the most active research laboratories (or "Kouza" in Japanese) in the field of natural products chemistry. At that time, the group head of LCO was Professor Toshio Goto, and his associate group members were Tadao Kondo, Minoru Isobe, Shinichi Nakatsuka and Kunio Imai. An amazing scientific world was opened to a green boy during the golden age of organic chemistry at Nagoya University. A marvelous collection of the great professors were carrying out scientific research there, including Yoshimasa Hirata, Toshio Goto, Kiyoyuki Yamada, Ryoji Noyori and Hisashi Yamamoto, along with Takayuki Shioiri in Nagoya City University. During the period from 1979 to 1986 at LCO, the foundation of my career as an organic chemist was established and, in particular, my thesis studies focusing on the synthesis of okadaic acid forged my chemical personality.[63] However, during this macho synthetic study, I felt unsatisfied, because okadaic acid ($C_{44}H_{68}O_{13}$) contains no nitrogen. During these days as an immature scientist, I hoped to do future research work in the field of nitrogen-containing natural product synthesis. This taste might have been guided by the influence of Toshio Goto, who was interested in the nitrogen-containing and highly oxygenated natural products. Yoshito Kishi, Fumiaki Nakatsubo and Tohru Fukuyama, a former stuff member and former students in the LCO, reported an astonishing masterpiece collection of the total syntheses of nitrogen containing natural products, such as tetrodotoxin, sporidesmin A, gliotoxin, saxitoxin, mitomycins and etc.

In 1987, I started my academic career at the Faculty of Education in Mie University, and embarked on the synthetic studies of nitrogen-containing natural products. During the period at Mie University from 1987 to 1991, we accomplished synthesis of nitrogen-containing natural products, such as (±)-aminobisabolenes **119**,[64] theonelline isocyanide **121**[65] and (±)-geranyllinaloisocyanide **122**[66] (Figure 9). The nitrogen in aminobisabolenes is considered to be generated through hydrolysis of the corresponding isocyanide **120**.

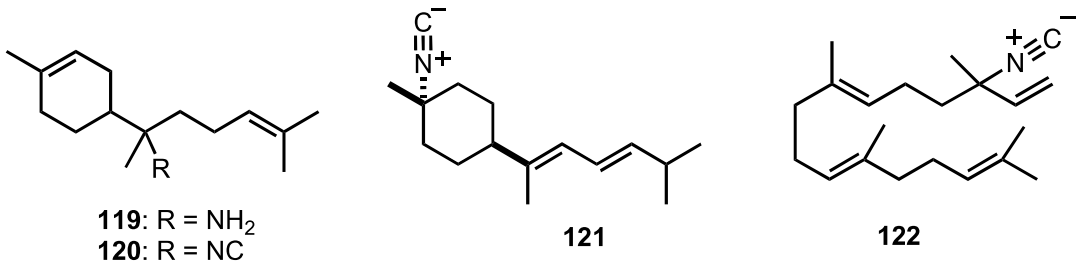
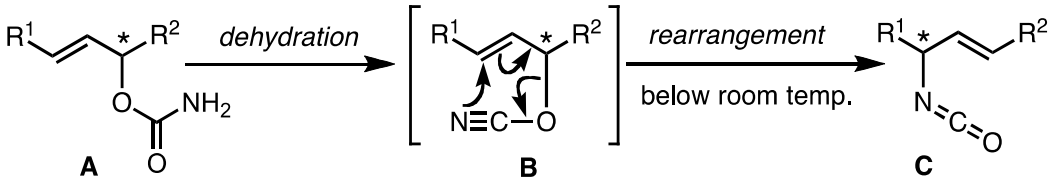


Figure 9. Structures of (±)-Aminobisabolenes, Theonelline Isocyanide and (±)-Geranyllinaloisocyanide

In addition to studies concentrating on natural product synthesis, I succeeded in the development of the allyl cyanate-to-isocyanate rearrangement (Scheme 39, **B** → **C**) as a useful tool for the synthesis of allyl

amines.[67] The key in this reaction is a facile dehydration of allyl carbamate **A** to generate allyl cyanate **B** which spontaneously undergoes a concerted [3.3] bond reorganization below ambient temperatures to furnish allyl isocyanate **C** with a high degree of [1,3]-chirality transfer.



Scheme 39. Ichikawa Rearrangement[68]

Again, 'Why isocyanates and isocyanides ?' The answer to this question may be found in the following statement, '· · · · · Leopold Ruzicka's assertion that a researcher doesn't look for problems to tackle, but that problems find those who will work on them · · · · ·'.[69]

ACKNOWLEDGEMENTS

The studies described in this manuscript became a reality owing to the extensive experimental work conducted by several students to whom I owe my deep gratitude and thanks. Financial support from The Kochi University President's Discretionary Grant is greatly appreciated.

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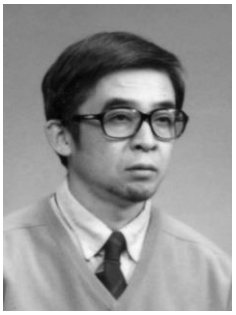

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