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Stereocontrolled synthesis and cyclization reactions of \( C \)-linked glycosylalkenes and \( C \)-linked glycosylalkadienes

Cui, Jingrong, Ph.D.
The Ohio State University, 1994
STEREOCONTROLLED SYNTHESIS AND CYCLIZATION 
REACTIONS OF C-LINKED GLYCOSYLALKENES AND C-LINKED 
GLYCOSYLALKADIENES

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of 
Philosophy in the Graduate School of The Ohio State University

By

Jingrong Cul, M.S.

The Ohio State University
1994

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To my parents and husband
ACKNOWLEDGMENTS

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VITA

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A. Recent Developments in Synthesis of C-Linked Glycosyl Compounds

C-Linked glycosides are important carbohydrate derivatives. They are produced when the anomeric oxygen of a glycoside is replaced by a carbon atom. They have drawn considerable interest in carbohydrate, enzymatic, and metabolic chemistry, as well as in organic synthesis in the past decade. C-glycosyl compounds occur as subunits in a variety of natural products, such as in palytoxin, the antifungal antibiotic 5,6-dihydroxypolyangioic acid, ezomycin and lasalocid A. Vienomycin, isolated from Streptomyces matensis venous, is an C-glycosylarene. C-Glycopyranosyl compounds act as enzyme inhibitors, particularly as inhibitors of glycosyltransferases and glycoside hydrolases. Shulman et al. synthesized epoxy-(β-D-glucopyranosyl)ethanes and 1,2-epoxy-3-(β-D-glucopyranosyl)propanes as irreversible inhibitors of β-D-glucosidase. C-β-D-galactopyranosylformamides were prepared as stable reversible inhibitors of the neutral β-D-galactosidase of E. Coli LacZ. Myers reported that β-D-galactopyranosyl and β-D-glucopyranosyl ketones would be useful as enzyme-activated irreversible inhibitors (suicide substrates) of glycosidas.

There is great interest in the use of C-linked disaccharides for
enzymatic and metabolic studies.\textsuperscript{10} When the oxygen linkage in a disaccharide is replaced by a methylene group, a \textit{C}-linked disaccharide is formed, which is no longer cleavable by hydrolysis. The first synthetic approach for \textit{C}-disaccharides was presented by Rouzand and Sinäy, who synthesized a protected "methyl \textit{C}-gentiobioside" from tetra-\textit{O}-benzyl-\textit{D}-gluconolactone and a dibromomethylene derivative of \textit{\alpha-\textit{D}-gluco}-hexodialdose.\textsuperscript{11} Giese and coworkers obtained \textit{C}-2-connected \textit{C}-linked disaccharides employing a carbohydrate-derived \textit{\alpha}-methylene lactone through a free-radical method.\textsuperscript{12} The synthesis of "\textit{C}-sucrose" was reported by Kishi\textsuperscript{13} and the preparation of the structurally very similar 1-\((\textit{\alpha-\textit{D}}\text{-glucopyranosyl})\text{-1-deoxy-\textit{D}-fructose} was also reported by Nicotra and his coworkers.\textsuperscript{14} Recently Raadt and Stütz published an one-step synthesis of\textit{C}-linked disaccharide from carbohydrate allylsilanes and tri-\textit{O}-acetyl-\textit{D}-glucal.\textsuperscript{15} \textit{C}-Linked "glycosides" also serve as a readily accessible source of chiral synthons for organic synthesis.\textsuperscript{16} Optically pure, substituted cyclopentane derivatives of interest in synthesis of prostaglandin analogs have been obtained by stereocontrolled addition of cyclopentadiene to \textit{trans-\alpha,\beta}\text{-unsaturated sugar derivatives in Horton's group.\textsuperscript{17} Tirandamycin acid, an antibiotic that belongs to a small group of 3-acyltetramic acids, is of particular importance due to its powerful inhibition of bacterial DNA-directed RNA polymerase.\textsuperscript{18} \textit{C}-glycosyl compounds was obtained through the highly stereocontrolled Ireland ester rearrangement from a glycal, have been applied to the synthesis of tirandamycin acid.\textsuperscript{19} Tatsuta et al. have published the stereoselective total synthesis of pyrrolizidine alkaloid bases, (-)-rosmarinecine and (-)-isoretronecanol from \textit{D}-glucosamine.\textsuperscript{20}
1. Introduction of a Carbon–Carbon Bond at the Anomeric Center of Neutral Sugars

A wide variety of methods for carbon-carbon bond formation at the anomeric carbon of neutral sugars have been developed. α-C-Glycopyranosyl derivatives of neutral sugars are readily accessible using both Lewis-acid catalyzed nucleophilic addition and radical-promoted addition to the anomeric center of an appropriately activated carbohydrate derivatives. The methodology to synthesize "C-glycosides" based on transition metals (palladium, manganese, rhodium and cobalt) has been developed recently. Concerted reactions such as [4+2] cycloadditions and sigmatropic rearrangements has also been employed to make "C-glycosides". The development in the synthesis of "C-glycosides" has been reviewed recently by Postema and Herscovici.

Lewis acid-catalyzed nucleophilic addition is the most popular method for carbon-carbon bond formation at the anomeric center for neutral sugars. The methodology relies on the natural electrophilicity of the anomeric center. A Lewis acid is usually used to form an oxonium ion species, which is then captured by an external carbon nucleophile. The most frequently used carbon nucleophiles include allylsilanes, allylstannanes, silylenolethers, 1,3-dicarbonyl compounds, aromatics, and organometallics. Different sugar derivatives have been utilized in "C-glycoside" synthesis, such as lactols, esters, glycosides, glycosyl halides, lactones, imidates, glycals, enitols and 1,5-anhydro sugars.

In 1988 and 1989 Horton and coworkers reported the stereoselective synthesis of C-(D-glucopyranosyl)alkenes and C-(D-
glucopyranosyl)alkadienes.\textsuperscript{21a,b} \(\alpha\)-D-Glucopyranose pentaacetate was treated with allyltrimethylsilane and boron trifluoride etherate in acetonitrile to give 3-\((\text{tetra}-O\text{-acetyl-}\alpha\text{-D-glucopyranosyl})\text{-1-propene}\ (1)\) stereoselectively in good yield. Similar treatment of methyl \(\text{tetra}-O\text{-acetyl-}\alpha\text{-D-glucopyranoside}\) or \(\text{tetra}-O\text{-acetyl-}\alpha\text{-D-glucopyranosyl bromide}\) gave 1 in preference to its \(\beta\) anomer. The reaction of \(\alpha\text{-D-glucopyranose pentaacetate}\) with (\(\text{E}\))-\(\text{penta}-2,4\)-dienyltrimethylsilane afforded the readily polymerizable (\(\text{E}\))-5-(\(\text{tetra}-O\text{-acetyl-}\alpha\text{-D-glucopyranosyl})\text{-1,3-pentadiene}\ (2)\) (Scheme 1).

Lewis et al. reported that the reaction of 2,3,4,6-tetra-\(O\text{-benzyl-D-glucopyranose}\) (3) with allyltrimethylsilane in the presence of boron trifluoride etherate in acetonitrile gave 3-(\(\alpha\text{-D-glucopyranosyl})\text{-1-propene}\ (4)\) and the \(\beta\) anomer 5 (10:1) in 55% combined yield (Scheme 2).\textsuperscript{21c} The chemical yield of
the coupling reaction was improved to 80% yield by using the more-activated derivative 2,3,4,6-tetra-O-benzyl-1-O-p-nitrobenzoyl-α-D-glucopyranose.

Hosomi et al. investigated the allylation reaction of methyl α-D-glucopyranoside, methyl α-D-mannopyranoside and α-D-glycopyranosyl chlorides with allylsilanes. Activation of the anomeric center can be readily achieved by trimethylsilyl triflate or iodotrimethylsilane to give the corresponding C-allylated glycopyranosides stereoselectively (Scheme 3).

β-C-Glycopyranosyl derivatives can be obtained by treatment of 2,3,4,6-tetra-O-benzyl-D-glucopyranolactone (6) with allylmagnesium bromide and then
reduction with triethylsilane in the presence of boron trifluoride etherate (Scheme 4).\textsuperscript{21c}

Kobertz and his coworkers found that $\alpha$-linked $C$-glycopyranosyl aldehydes can epimerize to the more stable $\beta$-linked anomer under mildly basic conditions (Scheme 5).\textsuperscript{27}

Free radicals are reactive intermediates of considerable importance in the development of organic chemistry. Radical intermediates are essentially
orthogonal in reactivity towards many of the common functional groups, e.g. carbonyl, hydroxy, and amino group. For the past decade a number of research groups have contributed to the synthesis of "C-glycosides" of neutral sugars by free-radical methodology. The formation of C–C bonds via addition of an alkyl radical to an alkene has proved to be a very versatile method for the synthesis of certain target molecules under mild conditions. The method has been used to introduce C-C bond at the anomeric center of neutral sugars. Adlington et al. prepared the "C-glucoside" 11 by trapping the C-1 glucosyl radical 10 with methyl acrylate in the presence of triphenyltin hydride. The glucosyl radical 10 was produced from 2,3,4,6-tetra-O-acetyl-D-glucosyl derivatives as shown in Scheme 6, and it appeared preferentially to couple to give the axial product 11.

Giese published similar results at the same time. The reaction of 2,3,4,6-tetra-O-acetyl-D-glucosyl bromide with nBu3SnH in the presence of acrylonitrile or methyl acrylate afforded the C–C coupling product with the axial arrangement of the substituents at C-1. The radical denitration with Bu3SnH of nitropyranose derivatives 12, giving exclusively the "β-C-glycosides", as

\[ \text{Scheme 6} \]
shown in Scheme 7, is another example of the axial stereoselectivity of glycopyranosyl radicals.\textsuperscript{22c}

The stereoselectivity of C–C coupling to the pyranosyl radicals was, in most cases, remarkably high, but hexopyranosyl and pentopyranosyl radicals showed different selectivities.\textsuperscript{27} The investigation by Giese showed that the 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl radical reacted with acrylonitrile preponderantly to give an \(\alpha\)-glycosyl compound having the newly formed C–C bond in an axial disposition. The 2,3,4-tri-O-acetyl-D-xylopyranosyl radical gave an \(\beta\)-glycosyl compound having an equatorial C–C bond. With the 2,3,4,6-tetra-O-acetyl-D-mannopyranosyl radical, the axial acetoxy substituent, adjacent to the radical center at C-2, led exclusively to a compound having a \textit{trans} C–C bond, whereas the 2,3,4-tri-O-acetyl-D-lyxopyranosyl radical showed \textit{trans} and \textit{cis}-addition to acrylonitrile in a 7:3 ratio.

Allylation at the anomeric center of pyranosides or furanosides with trialkylallylstannes through free radical reaction was studied by Keck et al.\textsuperscript{22d} The results are shown in Scheme 8.
Scheme 8

Scheme 9
Stork recently reported a stereospecific synthesis of C-glycosides by intramolecular trapping of a radical at the anomeric center of a carbohydrate. The stereospecific introduction of a styryl group at the anomeric center of a particular carbohydrate was achieved by the radical-introduced cyclization of a 3-phenylethynyl group attached, via a temporary silicon connection, to a suitable hydroxy group of the carbohydrate as shown in Scheme 9.

As seen from the above examples, the major product of C–C coupling reactions to the anomeric radicals of glycopyranose leads stereoselectively to the α-product. An early explanation suggested that the interaction with the non-bonding electron pair on the ring oxygen atom makes the σ-radical more stable and more nucleophilic than the σ-radical. The σ-radical would lead to the α-product. The theory of an σ-configuration at the radical center could not explain the different stereoselectivity of C–C coupling reaction to the anomeric radicals from different parent sugars. In most carbon-centered free radicals, the unpaired electron occupies an orbital which has mainly ρ-character (i.e., they are π-radicals) and is attacked from two sides. The observed high stereoselectivity requires that the radicals react from preferred conformations and be attacked predominantly from one side. The
stereoselectivity of six-membered cyclic radicals will be determined by three factors: (1) torsional effects; (2) steric substitute effects. (3) stereo-electronic effects. The torsional effect favors the axial attack at the radical center and is counteracted by the 1,3-diaxial interactions which occur in axial attack. Substituents in six-membered rings in a β position with respect to the radical center lead to an increase in anti-attack. The carbohydrate radicals derived from positions C-2, -3, and -4 of various deoxypyranosanyl derivatives to a large extent prefer to retain the 4C1 chair conformation of their parent compounds, and the stereoselectivity is mainly determined by torsional and steric effects. The stereoselectivity of glycosyl radicals, in which the radical center is the anomeric carbon atom, is controlled by stereo-electronic effects. The stereo-electronic effects influence both the radical conformations and the direction of attack on the radicals. ESR studies by Giese indicated that the glucosyl radical exists in a slightly distorted B2,5 boat conformation, whereas the mannosyl radical remains in the 4C1 chair conformation of its precursor. In both radicals the neighboring acetoxy group at C-2 is in the axial position. The interaction of the SOMO (semi-occupied molecular orbital) in the radical with the LUMO (lowest occupied molecular orbital) of the neighboring
carbon-oxygen bond at C-2 will stabilize the conformation of the radicals. The interaction of the semioccupied orbital with the oxygen lone pair results in a higher SOMO energy, making the SOMO–LUMO stabilization more significant.\textsuperscript{35} The conformation of radicals 29 is influenced by the substituents X at C-2.\textsuperscript{36} The boat form 29b is energetically more favored than the chair form 29a for X = OR or F. When X = NHTos, D and C$_3$H$_7$, the stereoelectronic effect does not suffice to compensate for the increase of steric strain in the course of the chair-boat interconversion, and only the chair conformation 29a is observed in the ESR spectrum. The direction of attack on anomeric radicals is also influenced by stereoelectronic effects. The glycopyranosyl radicals 28 and 29a, which exist in the $^4C_1$ conformation, are attacked axially from $\alpha$-face.
The overlap between the nonbonding electron pair of the ring oxygen atom and
the unpaired electron of the radical center (or the newly formed bond) is
maintained en route to the transition state in the case of axial attack on the
radical 28 and 29a. As a result, only α-products are formed. In the case of
radicals in the boat conformation 27, the stereoselectivity is somewhat lower.
The decrease in stereoselectivity is probably due to the fact that boat
conformers are more flexible than chair conformers. There is only a small
energy difference between a B2,5 boat and a 1,4B boat. According to the
stereoelectronic effect, B2,5 conformers afford α-products, whereas β-products
are formed from 1,4B conformers.

2. Introduction of a Carbon–Carbon Bond at the Anomeric Center of
2-Amino-2-Deoxy Sugars

Amino sugars are important molecules in Nature. They are constituents
of important natural products, such as aminoglycoside antibiotics, antigenic
determinants, glycoproteins, and glycolipids. D-Glucosamine, the first amino
sugar to be discovered, is one of the most abundant monosaccharides. It
occurs as a major constituent in the hard shells of crustaceans and other
arthropods, in many fungi, and it is distributed in higher animals as a constituent
of numerous glycosaminoglycans and glycosaminoglycuronans. The amino
"C-glycosides" are interesting molecules as they may show different biological
profiles because of the stability of the carbon-carbon bond at C-1. However,
their biological profiles have been scarcely evaluated, principally due to a lack
of suitable methods for their preparations. Silyl-based methodology, one of the
most successful methods for the stereoselective synthesis of C-(D-
glycopyranosyl)alkenes of neutral sugars, can only be applied to sugars having non-participating groups at C-2. Attempts by Horton et al. to obtain C-(d-glycopyranosyl)alkenes of 2-amino-2-deoxy-D-glucose by allyltrimethylsilane in the presence of BF$_3$·OEt$_2$ using several different protecting groups for the amino function were unsuccessful.$^{21b}$ The reaction of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-(p-toluenesulfonamido)-D-glucopyranose with allyltrimethylsilane in the presence of BF$_3$·OEt$_2$ in acetonitrile did not give an allylation product at the anomeric center, but afforded a product formulated as the imidazoline 30 in ~20% yield (Scheme 10). The same compound was obtained in almost quantitative yield when allyltrimethylsilane was not present in the reaction mixture. Giannis and Sandhoff also reported the unsuccessful C-allylation of 2-

![Scheme 10](image)

amino-2-deoxy-D-glucose with allyltrimethylsilane and BF$_3$·OEt$_2$. The following N-protecting groups had been tried: acetyl, phthaloyl, trifluoroacetyl, tosyl, p-methoxybenzylidene, benzylodxycarbonyl, tert-butyloxy carbonyl, in
combination with different Lewis acids: BF$_3$OEt$_2$, SnCl$_4$, AlCl$_3$, FeCl$_3$ and ZnI$_2$. Nicotra et al. found that the main procedures which allowed them to obtain $\alpha$-$C$-glucopyranosides, such as the reaction of a suitably protected glucopyranose with a Wittig reagent and the subsequent electrophilic-cyclization of the product, or the Lewis acid-catalyzed reaction of the appropriate glucopyranosyl derivative with allyltrimethylsilane, were unsuccessful when applied to many D-glucosamine derivatives.$^{38}$

There are a large number of publications about the synthesis of "$C$-glycosides" of neutral sugars, but only a few reports have been published, hitherto, on the synthesis of D-glycosamine "$C$-glycosides". In 1983, Nicotra and his coworkers reported the first example of stereospecific synthesis of an $\alpha$-$C$-glycosyl derivative of 2-amino-2-deoxy-D-glucose.$^{39}$ The synthesis was based on a Wittig reaction. A solution of 2-acetamido-4,6-0-benzylidene-2-deoxy-D-glucopyranose (31) in acetonitrile containing 2 equiv. of (ethoxycarbonylmethylene)triphenylphosphorane was boiled for 30 h. Flash chromatography of the crude product gave ethyl (2-acetamido-4,6-0-
benzylidene-2-deoxy-α-D-glucopyranosyl)acetate (32) in 50% yield (scheme 11). Giannis and Sandhoff used the same methodology to prepare ethyl (2-acetamido-2-deoxy-4,6-O-ethylidene-α,β-D-glucopyranosyl)acetate.40 However, the reaction was not stereospecific and the product was obtained not in a single step as reported by Nicotra, instead in two steps (Scheme 12). At first the Wittig reaction gave the ring opening alkene 34 in 92% yield, which was then treated with base for a short time (5–15 min) to afford major "α-C-glucoside" 35 (α:β 9:1), and for a long time (25–36 h) to give major "β-C-glucoside" 36 (α:β 3:10).

Scheme 12
In 1989 Nicotra et al. reported a new procedure for the synthesis of D-glucosamine "α-C-glycosides". The reaction of (2,3,5-tri-O-benzyl-D-arabinofuranosyl)benzylamine (38) with vinylmagnesium bromide afforded the 3-benzylamino-1,2,3-trideoxy-4,5,7-tri-O-benzyl-D-gluc-hept-1-enitol (39) and its diastereoisomer 40 in 71% yield and 88% diastereoisomeric excess. The

Scheme 13
cyclization of 39, to afford the "C-glycoside", was effected with Hg(CF₃CO₂)₂. It
gave stereoselectively the "α-C-glucoside" 41 in 77% yield and also the β-
anomer 42 in 20% yield as shown in Scheme 13.

Grondin et al. converted a 1-alkylglucal to 2-amino-2-deoxy C-glucosides
via [4+2] cycloaddition with bis(2,2,2-trichloroethyl)azodicarboxylate as shown
in Scheme 14.41 This method can be extended to the synthesis of 2-amino-2-
deoxy-C-glycosyl spiroketals.
Bertozzi and Bednarski reported the preparation of 2-azido C-glycosyl sugars by the direct Lewis acid-catalyzed addition of alkylsilanes to the nitrate glycosides of 2-azido sugars. Azides are stable under acidic and basic conditions and ideal amine equivalents. Both 2-azido sugars 47 and 48, which were prepared by azidonitration of the corresponding tri-O-benzyl-glycals, were treated with 1.5 equivalents of allyltrimethylsilane and 1.1 equivalents of BF$_3$·OEt$_2$ at 0 °C for 15 h to afford a 5:1 mixture of α/β C-glycosyl propenes 49 and 50. Both compounds 49 and 50, however, reacted readily at room temperature.
temperature to the 1,3-dipolar adducts to give 51. Ozonolysis of compounds 49 and 50 in dichloromethane at -78 °C followed by reduction with triethylamine provided the stable α-linked aldehydes 52 (Scheme 15).

In 1991, Giese reported the synthesis of an α-C-glycopyranosyl derivative of 2-amino-2-deoxy-D-mannose by a free-radical procedure (Scheme 16). The axial non-participating phthalimido group at C-2 had little influence on the reaction course and the reaction was similar with that of D-mannose derivatives.

B. Diels–Alder Reactions in Carbohydrate Chemistry

The efficient construction of enantiomerically pure, structurally complex molecules is a fundamental challenge in organic synthesis. Since its discovery in 1928 the Diels–Alder reaction has played an important role in the development of synthetic, mechanistic and theoretical organic chemistry. The remarkable stereo- and regio-selectivities which are associated with the cycloaddition, and the multiplicity of structural variations that are permitted to the
diene and dienophile components, are responsible for its exceptional synthetic value. The recent development in Diels–Alder reactions includes the design of chiral dienophiles, dienes and Lewis acid catalysts to improve the reactivity, regio- and stereo-selectivities. Cycloaddition reactions of carbohydrate derivatives have drawn much attention recently. Carbohydrates are inexpensive and renewable natural products, which contain numerous functional groups and chiral centers. Due to their pronounced complexing abilities and their content of chiral information, carbohydrates are applied as chiral auxiliaries in Diels–Alder reactions. Kunz investigated the Diels–Alder reactions of acrylates with carbohydrate auxiliaries. 3-O-Acryloyl-1,2-O-isopropylidene-α-D-glucofuranose (55) was silylated to give 56, which reacted
with TiCl₄ at -78 °C to give complex 57. Addition of cyclopentadiene gave exclusively the *endo* products 58 and the (1′′S, 2′′S)-diastereomer of 58 (93:7). Reaction of 56 with 1,3-cyclohexadiene, 1,3-butadiene and anthracene were less efficient (r. t., 12 d, yields<30%) and less diastereoselective. Cyclopentadiene reacted with the analogous α-xylofuranose-derived complex at -78 °C to afford a single diastereoisomer in 73% yield.

In the work relating to the total synthesis of (+)-4-demethoxy-daunomycinone, Stoodley and coworkers prepared the D-glucose-based diene as the key step for an anthracycline synthesis. Addition of the epoxytetrone
dienophile 60 to diene 59 gave a mixture of adducts 61 and 62 in ratios of 4:1 (C₆H₆, 5 °C) up to 7:1 (acetone, 5 °C). The major isomer 61, isolated by crystallization, was then converted into (+)-4-demethoxy-daunomycinone via glycoside cleavage with 0.5 N HCl in EtOH/H₂O (1:1, reflux, 30 h).

Diels–Alder reactions of carbohydrate derivatives constitute a useful methodology for the synthesis of carbocyclic compounds in optical active form, which have been used as intermediates in approaches to complex natural products, for example, prostaglandins,⁵⁰ the aureolic acid antibiotic olivin,⁵¹ the antibiotic actinobolin,⁵² and the diterpene forskolin.⁵³ Horton developed the use of acyclic sugar dienophiles to synthesize optically pure, substituted cyclopentane derivatives, which are of interest in the synthesis of prostaglandin analogues.⁵⁰ Methyl (E)-4,5,6,7-tetra-O-acetyl-2,3-dideoxy-D-arabino-hept-2-enonate (63), obtained by Wittig addition of Ph₃PCH₂CO₂Me to aldehyde-D-arabinose tetraacetate, reacted with cyclopentadiene in boiling

![Scheme 19](image-url)
toluene to give 40% of a crystalline, norbornene adduct 64 having 5S-exo ester, 6S-endo sugar-chain configuration. The absolute configuration of 64 was unambiguously confirmed by X-ray crystallographic analysis. When methyl (E)-4,5,6,7-tetra-O-acetyl-2,3-dideoxy-L-arabino-hept-2-enonate was subjected to the Diels–Alder reaction with cyclopentadiene under catalysis by aluminum chloride, four diastereoisomers were produced, and the pure diastereomer 65 was separated in 36% net yield. Oxidative double-bond cleavage of the (6S)-exo side-chain, (5S)-endo ester adduct 65 with osmium tetroxide–sodium metaperiodate, followed by reduction with sodium borohydride and by acetylation, gave 65% of the crystalline, chiral tetra-C-substituted cyclopentane
derivative 66. Compound 66 has the correct relative stereochemistry of all five chiral centers of 9, 11-dideoxy-9,11-bis(hydroxymethyl)prostaglandin F₁α and also the same absolute stereochemistry as those corresponding centers in prostaglandin F₁α itself.

Horton and his coworkers investigated the carbocyclization of a D-glucose-derived alkene. The "diacetone" D-glucose-derived alkene, 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enofuranose, reacts with cyclopentadiene under catalysis by ZnCl₂ of diethyl ether solution in benzene during 1 h at 45 °C to afford 34% of a dextrorotatory product 67. Accompanying 67 is 16% of an isomeric, laevorotatory product 68, along with 3% of an additional isomer 69 and a very low proportion of a fourth isomer 70.

\[
\text{Scheme 21}
\]
Formation of the products observed in this reaction may be rationalized as resulting from net deacetonation of the starting alkene, migration of the double bond to the 2,3-position with generation of carbonyl functionality at C-4 and C-1, together with cycloaddition to the 2,3 double bond and internal acetal formation between C-1 and O-5 and O-6.

Fraser-Reid and coworkers investigated the behavior of "diacetone" glucose-derived dienes in Diels–Alder reactions. The diene 71, prepared from "diacetone-D-glucose", was treated with maleic anhydride in refluxing toluene for 10 h, then a single product 72 was obtained after chromatography in 86% yield. The addition had occurred exclusively from the convex surface of 71 and was entirely endo selective. Giuliano investigated Diels–Alder reactions of analogous six-membered dieno-pyranosides 73—78 with different patterns of substitution on the pyranose ring. This new class of dienes underwent cycloaddition with maleimide or its N-phenyl derivative to give the annulated pyranosides. The Diels–Alder reactions were highly stereoselective,
giving single products in some cases. There was a strong preference for the formation of products resulting from addition of the dienophile to the face of the diene opposite the anomeric center.

\[
\begin{array}{ccc}
\text{73} & \text{74} & \text{75} \\
\text{MeO} & \text{MeO} & \text{MeO} \\
\text{OMe} & \text{OMe} & \text{OMe} \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{76} & \text{77} & \text{78} \\
\text{BnO} & \text{MeO} & \text{BnO} \\
\text{OMe} & \text{OMe} & \text{OMe} \\
\end{array}
\]

The Diels–Alder reaction is strongly influenced by the medium effects, such as high pressure, ultrasound, aggregation effects in water, adsorption on dry SiO₂ or clays and zeolites. Introduction of sugar moiety in organic dienes and dienophiles will improve their solubilities in water, induce chirality and allow the cycloaddition reaction run in water. Lubineau and Queneau published their studies of the use of glycoorganic compounds to perform [4+2] cycloadditions in water as solvent.⁵⁷ Because of the hydrophobic effect, the cycloaddition reaction was run in very smooth conditions (room temperature, neutral) and gave a virtually complete endo selectivity. The "1,3-butadienyl β-D-glucoside" 79 reacted with methacrolein in water at 20 °C for 3.5 h to afford the endo adducts 80a and 80b in a 60:40 ratio. The sugar moiety is readily removed by
acidic hydrolysis or using glycosidase in neutral conditions at room temperature.

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{CH}_3 & \quad \text{CHO}
\end{align*}
\]

\[79 \rightarrow 80a + 80b\]

\[\text{H}_2\text{O}, 3.5 \text{ h}, 20^\circ\text{C}\]

Scheme 23

C. Aminoglycoside Antibiotics

Since discovery of streptomycin by Waksman in 1944, many aminoglycoside antibiotics have been found in microbial cultures. They are useful for treatment of bacterial infections and used as important chemotherapeutic agents. Naturally occurring aminoglycoside antibiotics can be divided into three major groups as follows:

1. Aminoglycosides containing streptomycin and its related aminocyclitols: streptomycins, spectinomycins, neomycins, kanamycins, neamines, destomycins, and fortimicins.
2. Aminoglycosides containing cyclitols and monoaminocyclitols: kasugamycins, myomycins, LL-BM123α, and validamycins.


These naturally occurring aminoglycoside antibiotics have been reviewed by Umezawa, Cox and Hooper. Among them, kanamycins are commercially available as chemotherapeutic agents in treating infections. The structure of kanamycins includes pseudotrisaccharides containing the 4,6-disubstituted 2-deoxystreptamine, and the two carbohydrate components are

![Figure 1. Structures of Kanamycins](image-url)

<table>
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<tr>
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<th>R³</th>
<th>R⁴</th>
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<tr>
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<td>H</td>
<td>NH₂</td>
<td>NH₂</td>
<td>OCONH₂</td>
</tr>
</tbody>
</table>
linked in the $\alpha$-form at C-4 and C-6 positions of the 2-deoxystreptamine moiety as shown in Figure 1. Kanamycin A was found in the culture filtrate of *Streptomyces Kanamyceticus* together with kanamycins B and C as minor products. Kanamycin A is an important antibiotic agent against a variety of the Gram-positive and Gram-negative bacteria, especially against the mycobacteria, and now widely used as an antituberculosis agent. The structure of Kanamycin A was demonstrated independently by Japanese and American-Canadian groups, and the absolute configuration was established by Rinehart and Tatsuoka.

Many efforts to synthesize aminoglycoside antibiotics have been attempted. The total synthesis of kanamycin A was achieved by Nakajima and Umezawa soon after the structure of kanamycin A was determined, and kanamycin B and C were further synthesized by Umezawa et al. in 1968. Starting from the synthesis of pseudodisaccharides paromamine and neamine, more-complex aminoglycosides, kanamycins, tobramycin, tutirosin B, neomycin C and so on were synthesized successively. Nakajima and coworkers synthesized kanamycin A by condensation of 4-$O$-(6-acetamido-2,3,4-tri-$O$-benzyl-6-deoxy-$\alpha$-$D$-glucopyranosyl)-1,3-di-$N$-benzyloxycarbonyl-2-deoxystreptamine (81) with 3-acetamido-2,4,6-tri-$O$-benzyl-3-deoxy-$\alpha$-$D$-glucopyranosyl chloride (82) to give the protected kanamycin A (83), which led to kanamycin A after deprotection (Scheme 24). Umezawa synthesized kanamycin A by coupling 6-$O$-(3-amino-3-deoxy-$\alpha$-$D$-glucopyranosyl)-2-deoxystreptamine with 6-amino-6-deoxy-$D$-glucose by way of their suitably protected derivatives. In the total synthesis of aminoglycosides, the formation of a glycosidic linkage in a stereoselective manner and selective blocking(s) of amino and/or hydroxy groups are prerequisites.
The antibacterial spectrum of the early aminoglycoside antibiotics was limited by bacterial resistance. Studies\textsuperscript{71} on the biochemical mechanisms of resistance to aminoglycoside antibiotics showed that the most important mechanisms of resistance to aminoglycoside antibiotics among resistant bacteria of clinical origin are due to enzymatic inactivation by phosphorylation and adenylylation of the hydroxy group, and by acetylation of the amino group on the specific positions. A common mechanism of inactive of kanamycins, neomycins, paromomycins, and ribostamycin by a number of resistant bacteria is phosphorylation of the 3'-hydroxy group of these antibiotics, which suggested that modification of the 3'-hydroxy group might lead to derivatives that would be active against resistant bacteria. Umezawa and coworkers synthesized 3'-O-
methyl-kanamycin A 84\textsuperscript{72} and 3'-deoxykanamycin A 85,\textsuperscript{73} respectively. The functionalization of the 3'-hydroxy group caused a remarkable effect on the antibacterial activity. The 3'-deoxykanamycin A 85 was as active as the parent antibiotic, but it was also active against both *Escherichia Coli* carrying R factor and resistant *Pseudomonas*, which inactivate kanamycin A by the 3'-O-phosphorylation mechanism. The 3'-O-methylkanamycin A 84 was almost inactive, suggesting that, although the 3'-hydroxy group does not play an important role in the mechanism of antibacterial action, there is a strong steric factor associated with the methoxy group. 3',4'-Dideoxykanamycin B (86)\textsuperscript{74} has significant activity against common bacteria and resistant bacteria,
including various strains of *Escherichia coli* carrying R factor and *Pseudomonas*. Another form of enzymatic inactivation of aminoglycoside antibiotics is *N*-acetylation. As reported by Umezawa and coworkers, the inactivated product of kanamycin A is its 6'-*N*-acetyl derivative. Therefore, modification of the 6'-amino group was introduced. Selective 6'-*N*-benzyloxycarbonylation was achieved by use of benzyl *p*-nitrophenylcarbamate, to give 87 in a yield of 60%. The benzyloxycarbonyl group was reduced to a methyl group by lithium aluminum hydride, to afford 6'-*N*-methylkanamycin A 88, which showed activity at the same level as the parent substance and was active against resistant bacteria producing the acetyl transferase. The acylation of the amino group on C-1 position with amino acids will inhibit kanamycin phosphate transferase. The kanamycin derivative named BB-K8 (89) was found to be active against both kanamycin sensitive and resistant organisms, inhibiting both kanamycin phosphate transferases I and II. BB-K8 (89) was synthesized by selective 6'-*N*-benzyloxycarbonylation of kanamycin A with *N*-(benzyloxycarbonyloxy)succinimide, followed by *N*-acylation with an active ester of L(-)-4-(benzyloxycarbonyl)amino-2-
hydroxybutyric acid and separation by chromatography. Configurational and positional isomers of BB-K8 (89) were also prepared. The analogues of kanamycin B, 3',4'-dideoxykanamycin B, tobramycin, paromomycin and neamine also showed improved activity against resistant organisms.
CHAPTER II

STATEMENT OF THE PROBLEM

The synthesis of C-analogues of glycosides has drawn more and more attention because of their biological interest and their applications in organic synthesis. Numerous methods have been developed for the stereocontrolled synthesis of C-glycopyranosyl derivatives of neutral sugars. Unfortunately, amino and amido substituents at C-2 are incompatible with most of the conditions used. Only five reports have been published, hitherto, on the synthesis of D-glucosamine C-glycosyl compounds. The published methods for the synthesis of 2-amino C-glycosyl compounds suffer disadvantages of several steps, expensive starting materials and low stereoselectivity. One of the objectives in this investigation is to design and develop an efficient and economic methodology to introduce, stereoselectively or stereospecifically, a C-C bond at the anomeric center of 2-amino-2-deoxy sugar derivatives from cheap and natural abundant amino sugar compounds.

The Lewis acid-catalyzed allylsilyl methodology is the most common and important method to introduce a C-C bond at the anomeric center for neutral sugars. The reaction course and stereoselectivity are influenced by different substituents at the anomeric center, by different protecting groups, by reaction temperature and solvents. It is important to find the best conditions to produce
the C-glycosyl derivatives of neutral sugars with high yields and high stereoselectivity.

C-Linked oligosaccharides are now in high demand for studies of sugar metabolism, and as enzyme inhibitors. C-Analogues of aminocyclitol antibiotics may play an important role in investigation of the antibacterial mechanism of aminoglycoside antibiotics. No report has been published to approach the C-linked aminocyclitol antibiotics and their biological function has not been evaluated. The Diels–Alder reaction is a traditional way to construct the 6-carbocycles, this could be used to build up the 2-deoxystreptamine ring for the synthesis of C-analogues of aminocyclitol antibiotics. There are few reports concerning the Diels–Alder reaction of C-glycosyl compounds. As a methodology study, a series of C-glycosyl dienophiles and dienes are here to be synthesized, and their [4+2] cyclization reactions investigated in detail.

The objectives in this investigation are summarized as followings:

1. Design and develop a new methodology to introduce a carbon–carbon bond at the anomeric center of 2-amino-2-deoxy sugars from natural abundant amino sugars.

2. Modify the allylsilane methodology to introduce a carbon–carbon bond at the anomeric center of neutral sugars with high stereoselectivity and high yield.

3. Synthesize a series of C-linked glycosyl dienophiles and dienes to study their cyclization behaviors to approach the C-linked analogues of aminocyclitol antibiotics.
CHAPTER III

RESULTS AND DISCUSSION

A. Synthesis of C-linked Glycosyl Compounds from 2-Amino-2-Deoxy Sugars and Neutral Sugars

The amino function or a protected amino function at the 2-position of amino sugars has a strong neighboring-group participation effect and makes the chemistry of 2-amino-2-deoxy sugars quite different from that of neutral sugars. Most methodologies for introducing a C–C bond at the anomeric center for neutral sugars have failed for 2-amino-2-deoxy sugars. It is thus very important to develop an universal method for introducing C–C bond at the anomeric center of 2-amino-2-deoxy sugars from available natural and inexpensive starting materials with few steps. Free-radical reactions have the advantage of less influence from other functional groups, and such a procedure has been used to synthesize C-glycosyl derivatives of neutral sugars, but has not been applied to C-glycosyl derivatives of amino sugars. The use of free-radical reaction to synthesize C-linked glycosyl derivatives of 2-amino-2-deoxy sugars may avoid the participating influence from an amino function at the 2-position. A series of potential free-radical precursors have been synthesized from 2-amino-2-deoxy sugars. The course of the free-radical reaction and the
influence of protecting groups on the amino function and substituents at the anomeric center on the stereochemistry have been evaluated in detail. Various methods have been developed for the synthesis from neutral sugars of C-analogues of glycosides. Allylsilyl methodology is the most commonly used among these. It is important to find the best reaction conditions for the facile formation of the C-glycosyl bond with high yield and stereoselectivity.

1. **Allylation of 2-amino-2-deoxy-glucopyranosyl derivatives via a free-radical reaction**

   The radical chain allylation of organic halides and related precursors by allylstanne reagents is a powerful and selective method for introducing the allyl group into organic molecules. The overall transformation and the generally assumed mechanism are illustrated in figure 2. The trialkyltin radical as the chain-transfer agent is generated by addition of an alkyl radical to the allylstanne reagent, followed by a fragmentation reaction. The net result is overall allylation of a suitable radical precursor. The following factors are important in design of a successful, high-yielding, free-radical chain process:

   1. Specific generation of initiator radicals,
   2. Selective, low energy pathways for the production of substrate radicals,
   3. Chain carrying steps with reagents that preclude the formation of highly reactive, indiscriminate radicals,
   4. Reasonable termination steps to produce innocuous by-products which do not disturb the chain.

   A competing reaction in the radical chain allylation is the addition of the
nucleophilic radicals to the newly formed allylated product. According to Curran, the reaction constant $k_a$ for the addition of alkyl radicals to allylstannanes is approximately $10^4$–$10^5$ M$^{-1}$S$^{-1}$, and allylstannanes are at least one order of magnitude more reactive than simple alkenes toward alkyl radicals. This modest activation ensures that the starting allylstanne is more reactive than the allylated product and it aids in propagating chains.

For free-radical allylation reactions at the anomeric center of sugar compounds, appropriate glycosyl halides and acylthio derivatives may be employed as substrates, provided that these intermediates are reasonably stable and can be obtained in pure form. The acetylated 2-amino-2-deoxy-$\alpha$-glucopyranosyl chloride, bromide, and xanthate derivatives were here...
investigated as possible free radical precursors for the allylation reaction at the anomeric center of 2-amino-2-deoxy-D-glucose.

\[
\begin{align*}
\text{HO-CH(OH)O} & \quad \text{HO-CH(OH)O} \\
\text{HCl-H}_{2}\text{N} & \quad \text{AcHN} \\
\text{90} & \quad \text{91} \\
\text{HO-CH(OH)O} & \quad \text{HO-CH(OH)O} \\
\text{AcHN} & \quad \text{AcHN} \\
\text{91} & \quad \text{92} \\
\end{align*}
\]

i) 1 equiv. Na in methanol. ii) 1 equiv. Ac\(_2\)O. iii) AcCl.

Scheme 25

Preparation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-\(\alpha\)-D-glucopyranosyl chloride (92). The commercially available D-glucosamine hydrochloride (90) was converted into 2-acetamido-2-deoxy-D-glucopyranose (91) by the well-established method of Horton\(^84\) in 91% yield. 2-Aacetamido-3,4,6-tri-O-acetyl-2-deoxy-\(\alpha\)-D-glucopyranosyl chloride (92) was prepared following the procedure of Horton\(^85\) in 73% yield. Compound 91 was suspended in acetyl chloride until a clear viscous solution resulted. If the solution was cloudy, a side product (\(\alpha\)-D-glucosamine pentaacetate) could be detected in the product. After conventional processing of the reaction solution and recrystallization from anhydrous diethyl ether, compound 92 was obtained as a pure white crystalline compound having physical constants in good agreement with the literature values.
Preparation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl bromide (94). Treatment with hydrogen bromide–acetic acid converted α-D-glucosamine pentaacetate (93) into 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl bromide (94) in 90% yield. Compound 94 was not stable and was used directly without further purification.

Free-radical mediated C-allylation of compounds 92, 94, and 97: Synthesis of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (95) and 3-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-1-propene (98). 2-Acetamido-2-deoxy-D-glucopyranosyl derivatives are the most conveniently prepared among protected 2-amino-2-deoxy-D-glucoses. It was therefore considered logical to evaluate first the free-radical reactivity of 2-acetamido-2-deoxy-D-glucopyranosyl derivatives having different activating groups at the anomeric center.

Stereocontrolled synthesis of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (95). The reaction of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride (92) with allyltributyltin (3 molar equiv.) in the presence of the radical initiator AIBN (0.15 molar equiv.) in dry
Scheme 27
toluene for 8 h at 85 °C under Ar produced 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (95) as a white solid in 67% yield after purification on a column of silica gel. After recrystallization from 3:1 hexanes-EtOAc, white needles having mp 109-110 °C, [α]D +47° in chloroform were obtained. The β-anomer of 95 was detected by NMR methods in 2% yield in the mother liquor, although the pure β-anomer of 95 could not be obtained through conventional recrystallization and chromatography of the mother liquor. Polymerization was the major competing reaction and a polymeric material was obtained in 24% yield. The presence of dimer and trimer analogues of the C-glycosyl derivative 95 could be demonstrated from the mass spectrum of the polymer. The oxazoline 96 was a side-product isolated in 5% yield; it presumably arises via competing attack of the 2-acetamido group on a glycosyl radical intermediate.

The preparation was readily conducted on a 10-gram scale. Freshly prepared 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride used as starting material gave the best yield. It was found that the presence of α-D-glucosamine pentaacetate in the starting material did not influence the free-radical reaction and it could be recovered after reaction. The yield of product 95 was increased from 40 to 67% by increasing the amount of allyltributyltin from 2 molar equivalents to 3 molar equivalents. When the amount of initiator (AIBN) was decreased from 0.15 to 0.075 molar equivalent, the yield was decreased from 67 to 26%. If the volume of toluene solvent was doubled, the yield decreased from 67 to 49%.

In the free-radical allylation reaction of the acetylated 2-amino-2-deoxy-D-glucosyl chloride derivative (92) with allyltributyltin, the major competing reaction was addition of the glycosyl radical to the product alkenes to give
oligomers and polymers. Increasing the molar equivalent of allylstanne reagent was expected to favor the addition of glycosyl radicals to allylstannes rather than to the allylated product, and as a result, the extent of the polymerization reaction was decreased. Radical chain reactions, such as the radical addition of alkyl halides to alkenes in the presence of tributyltin hydride, requires the maintenance of a low concentration of radicals over the course of a reaction. Most free radicals are highly reactive species, and react with each other by combination or disproportionation at rates approaching the diffusion-controlled limit. However, in the radical allylation chain-reaction, low concentrations are not required (0.5 M is typical), since no tin hydride is present and intermediate radicals are not intercepted by hydrogen-atom abstraction. In the free-radical allylation reaction of the 2-amino-2-deoxy-D-glucosyl chloride derivative, another competing reaction involves the 2-acetamido group, leading to the oxazoline product. Low concentrations should increase the intramolecular rearrangement reaction and depress the intermolecular free-radical allylation reaction. When the concentration of the derivative was decreased, the yield of oxazoline side-product was increased. Decrease in the amount of initiator also increases the competition leading to the oxazoline.

The structure of the derivative was determined by its satisfactory elemental analysis, by NMR spectra, by its specific optical rotation, and its mass spectrum. The α-anomeric configuration of the derivative was established on the basis of the small value (4.5 Hz) and a lower downfield chemical shift of H-1' (at δ 4.21) by comparison with the large value of 10.1 Hz and higher upfield chemical shift of H-1' (at δ 3.16) for the β-anomer of the derivative. The 1H-NMR spectrum of the derivative showed an apparent quintet (ddd, J 4.5, 4.8, 10.0 Hz) for H-1' at δ 4.21 and a doubled doublet of doublets (J 4.5, 8.2, 8.7 Hz) for H-2' at δ 4.52. The relatively
small values of $J_{2',3'}, J_{3',4'},$ and $J_{4',5'}$ (8.2, 6.8, and 6.8 Hz) for compound 95 in benzene-$d_6$ suggested that the conformation of the tetrahydropyran ring in the α-C-glycosyl-1-propene 95 was not the standard $^4C_1$ glycopyranosyl chair conformation and the ring is distorted and flattened, or the ring is in rapid equilibrium between the two chair conformers ($^4C_1$ and $^1C_4$).

The influence of different substituents at the anomeric center of 2-amino-2-deoxy sugars on the course and stereoselectivity of the free-radical reaction was investigated. The xanthate group is often used as a free-radical precursor and it was evaluated as a potential substituent at the anomeric center to generate the desired free-radical intermediate. 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl ethylxanthate$^{66}$ (97) in toluene was treated with 2 molar equivalents of allyltributyltin and 0.15 molar equivalent of AIBN at 80 °C overnight under Ar. The procedure afforded 95 stereospecifically, but only in 25% yield. Other products could not be purified and identified.

The ethylxanthate substituent was not as active as the chloride group for the production of glycosyl radicals, and it took overnight reaction to consume all of the starting material 97. The stereoselectivity at the anomeric center during the free-radical reaction was evidently not influenced by the configuration of the activating group on the anomeric center in the free radical precursor when the protecting group on the amino function was the same group. Both the α-substituted 2-amino-2-deoxy-D-glucopyranosyl chloride derivative (92) and the β-substituted xanthate derivative 97 favored production of the α-C-glycosyl product.

The carbon-bromide bond is much weaker than the carbon-chloride bond and it should thus be easier to produce free radicals from bromide-substituent precursors. 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-
glucopyranosyl bromide (94) was evaluated as a possible free-radical reaction precursor. However, under reaction conditions similar to those successfully used with the chloride 92 to produce the α-C-glycosyl product 95, the oxazoline compound 96 was obtained as the major product (88% yield), and the allylated compound 95 could not be found in the products. The acetamido group is an extremely efficient participative group and, in conjunction with bromide as a very good leaving group, causes the 1,2-cyclization reaction to dominate and give the oxazoline product 96. In contrast, chloride is not as active as bromide when functioning as a leaving group to produce an oxonium ion; thus chloride 92 gave the free-radical product 95 as the major product and the oxazoline 96 was obtained in only 5% yield.

![Scheme 28](image)

**Synthesis of 3-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-1-propene (98).** Deacetylation of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (95) with a catalytic amount of sodium methoxide in methanol gave 3-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-1-propene (98) in quantitative yield. Compound 98 was recrystallized from ethanol to afford
white crystals having mp 204–206 °C and [α]D +109° in methanol. When the deacetylation time was short, 3-(2-acetamido-6-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (98a) was present as a side product and could be separated in crystalline form by using a silica gel column. The yield of compound 98a was depended on the deacetylation time. In the 1H-NMR spectrum of compound 98a, there were two doublets for hydroxy groups at δ 5.15 and 4.87, and two singlets for methyl carbonyl groups at δ 1.98 and 1.82. The signal for N-H was at δ 7.70 as a doublet (J_NH₂ 7.8 Hz). One of the methyl carbonyl group belonged to the 2-acetamino function. The location of another methyl carbonyl group was decided according to the chemical shifts of H-6'a and H-6'b. The acetyl protecting group makes the chemical shifts of hydrogens connected with the same carbon more downfield. In compound 98a, the signals for H-1'-H-5' were between δ 3.87 and 3.11. However, the signal for H-6'a was appeared at δ 4.21 as a doubled doublet (J_6'a,6'b 11.6 Hz and J_5',6'a 1.9 Hz) and that for H-6'b at δ 4.04 as a doubled doublet (J_5',6'b 6.7 Hz), which indicated that the acetyl group was on C-6.
Preparation of 3,4,6-tri-O-acetyl-2-p-methoxybenzylideneamino-2-deoxy-α-D-glucopyranosyl bromide (100). Following the modified procedure of Umezawa,\textsuperscript{89} in these series, compound 100 was prepared from D-glucosamine hydrochloride (90). Treatment of 90 in 1 M NaOH solution with p-anisaldehyde and acetylation with acetic anhydride in pyridine solution gave the intermediate 99 in 77% yield, which reacted with 30 wt. % HBr in acetic acid to afford 100 having mp 110 °C (dec.) in 47% yield.

Free-radical C-allylation of compound 100: Synthesis of 3-(3,4,6-tri-O-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl)-1-propene hydrochloride (102). The p-methoxybenzylidene protecting group was examined as a route of access to C-glycosyl 2-amino sugar derivatives having the amino group free. The group is larger than the acetyl group and is a nonparticipating amino-protective group. It is very easy to remove under acidic conditions and is stable in basic conditions. The p-methoxybenzylidene-
protected 2-amino-2-deoxy-α-D-glucopyranosyl derivative 100 showed α-stereoselectivity at the anomeric center in the free-radical C-allylation reaction. Thus treatment of compound 100 with allylttributyltin (3 mol. equiv.) and AIBN (0.30 mol. equiv.) at 85 °C under Ar for 24 h produced 3-(3,4,6-tri-O-acetyl-2-deoxy-2-α-p-methoxybenzylideneamino-α-D-glucopyranosyl)-1-propene 101.

The 45% N-substituent was then hydrolyzed off in acidified acetone to give 102 as a white solid precipitate, mp 220–222 °C (dec.), [α]D +59° in methanol in 45% yield. Neutralization of 102 in dichloromethane with sat. NaHCO₃ provided 3-(3,4,6-tri-O-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl)-1-propene 102a as a syrup. The p-methoxybenzylidene protecting group is readily lost during the reaction or the purification of the product on a column of silica gel. The C-allylation reaction was slow, either because p-methoxybenzaldehyde quenched the radical center, or the large protecting group on the amino function slowed the reaction rate due to steric effects. The free-radical reaction took 24 h and AIBN was added to the system twice.
The α-anomeric configurational assignment of 102 was based on the small $J_{1',2'}$ coupling constant of 4.8 Hz. In the $^1$H-NMR spectrum of 102, the N-H signal appeared at the lowest field ($\delta$ 8.66) as a very broad single peak. The H-1' signal appeared at $\delta$ 4.44 as a doubled doublet of doublets ($J_{1',2'}$ 4.8 Hz, $J_{1',3a}$ 10.5 Hz, $J_{1',3b}$ 4.9 Hz) and H-2' at $\delta$ 3.79 as a doubled doulet ($J_{1',2'}$ 4.8 and $J_{2',3'}$ 8.8 Hz). The removal of the hydrochloride from 102 was demonstrated in the $^1$H-NMR spectrum of 102a by the change of chemical shift for N-H from $\delta$ 8.66 to $\delta$ 1.30. The coupling constants of compound 102 showed that the compound in chloroform solution existed essentially in the $^4C_1$ chair conformation ($J_{1',2'}$ 4.8 Hz, $J_{2',3'}$ 8.8 Hz, $J_{3',4'}$ 7.9 Hz, and $J_{4',5'}$ 8.0 Hz).
Preparation of 3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-\(\alpha\)-D-glucopyranosyl bromide (104). Compound 104 was prepared from 1,3,4,6-tetra-O-acetyl-2-deoxy-2-trifluoroacetamido-\(\alpha\)-D-glucopyranose (103) by a modification of the procedure of Wolfrom and Bhat. The trifluoroacetyl protecting group in 103 could be introduced by two different methods. 1,3,4,6-Tetra-O-acetyl-2-deoxy-2-p-methoxybenzylideneamino-\(\alpha\)-D-glucopyranose (99) was converted into 1,3,4,6-tetra-O-acetyl-\(\alpha\)-D-glucopyranose hydrochloride in 73% yield after treatment with acidified acetone, which was then treated with trifluoroacetic anhydride in
pyridine to give 103 in 83% yield.\textsuperscript{91} Compound 99 was not found to be the most convenient starting material, and 103 can alternatively be prepared directly\textsuperscript{92} from glucosamine hydrochloride 90. Compound 90 was neutralized with sodium methoxide solution and then treated with S-ethyl trifluorothioacetate to introduce the trifluoroacetyl protecting group. The intermediate was acetylated with acetic anhydride in pyridine to afford 103 as a 1:0.8 $\alpha,\beta$-mixture in 89% yield. Compound 103 was transformed in 93% yield into 104 by treatment with 30 wt. % HBr in acetic acid in 93% yield. Compound 104 had mp 94–96 °C and [\(\alpha\)]\textsubscript{D} +125.3° in chloroform.

Free-radical C-allylation reaction of compound 104:

\textbf{Synthesis of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-$\alpha$-$\text{D}$-glucopyranosyl)-1-propene (105).} The trifluoromethyl group is a strongly electron-withdrawing group, and greatly diminished the neighboring-group participation effect of the amino function in a trifluoroacetyl protecting group as compared with the acetamindo group. This consideration made the bromide derivative 104 attractive as a possible free-radical precursor, as compared with
2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl bromide (94), which produced exclusively the 1,2-cyclization product, oxazoline 96, during the attempted free-radical allylation reaction. The reaction of compound 104 with allyltributyltin (2 mol. equiv.) and AIBN (0.15 mol. equiv.) in dry toluene under Ar at 85 °C for 6 h gave the desired product 105 in 60% yield after chromatographic purification on a silica gel column. The β-anomer of 105 was produced in 5% yield in the crude product, but it could not be obtained in pure form. After dissolving the crude product in hot 4:1 hexanes–ether and collecting the early precipitated syrup, the pure compound 105 was obtained as a colorless syrup, which showed [α]D +22° in chloroform, and the β-anomer of 105 remained in solution with 105. The 1H-NMR spectrum of 105 in C6D6 showed quite unusual 1H-1H coupling constants for the hydrogens in tetrahydropyran ring (J1',2' 3.8 Hz, J2',3' 6.0 Hz, J3',4' 5.8 Hz, and J4',5' 4.6 Hz). The anomeric configuration of 105 cannot be attributed unambiguously by the J1',2' coupling constant and the [α]D value. To clarify this point, the syrupy product 105 was fully deprotected in saturated methanolic HCl solution and then acetylated with acetic anhydride and pyridine. After recrystallization, a white crystalline product was obtained, which was confirmed to be 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (95) by its melting point, specific rotation value in chloroform, and also its 1H and 13C-NMR spectra. As a result, the α-anomeric configuration of 105 was clearly demonstrated by the chemical transformation of 105 to the known propene derivative 95. The trifluoroacetamido group is slightly larger, but more polar than the acetamido group. The coupling constants of J1',2' 3.8 Hz, J2',3' 6.0 Hz, J3',4' 5.8 Hz, and J4',5' 4.6 Hz suggest that the tetrahydropyran ring of compound 105 is not exclusively in the normal chair conformation, but exists as a
conformational mixture in rapid equilibrium between $^4C_1$ and $^1C_4$ chair conformers, with significant population of the later, having all substituents axial except that at C-1.

\[ \text{OH} \quad \text{OAc} \quad \text{OAc} \]
\[ \text{ClH}_2\text{N} \quad \text{PhthN} \]
\[ \text{I}) \quad \text{II}) \quad \text{III}) \quad \text{IV}) \]

\[ \text{AcO} \quad \text{AcO} \quad \text{Br} \quad \text{Cl} \]

\[ \text{AcO} \quad \text{AcO} \quad \text{Cl} \quad \text{PhthN} \]

\[ \text{108} \]

Scheme 33

Preparation of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido-\(\beta\)-D-glucopyranose (106). Following the modified procedure of Lemieux, the phthaloyl protecting group on the 2-amino function was first introduced by reacting D-glucosamine hydrochloride with phthalic anhydride in methanolic sodium methoxide solution, and then the intermediate was acetylated with acetic anhydride in pyridine. Compound 106 was obtained in 42% yield, as \(\alpha,\beta\) mixture in the ratio of 1:8.
Preparation of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-
glucopyranosyl bromide (107). Bromination of compound 106 at the
anomeric center with 30 wt. % of HBr in acetic acid provided compound 107 in
65% yield. The mixture of α,β anomers of 107 (1:5) was used without further
separation and purification.

Preparation of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-
glucopyranosyl chloride (108). Compound 108 was prepared by the
procedure of Akiya and Osawa. Chlorine was introduced at the anomeric
center of compound 106 by treating it with anhydrous aluminum trichloride in
dry dichloromethane solution to give compound 108 in 70% yield.

Free-radical C-allylation reaction of compounds 107 and 108:
Synthesis of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-
glucopyranosyl)-1-propene (109). Phthalimido protection is well
established for 2-amino-2-deoxy sugars for introduction of a 1,2-trans-glycosidic
linkage in a nucleophilic addition-reaction. According to Lemieux\textsuperscript{93} the phthalimido group can participate in the overall reaction and thereby lead to a cationic intermediate which does not yield a stable orthoester, but blocks \(\alpha\) attack. The influence of phthalimido protection on the stereoselectivity at the anomeric center in the free-radical allylation reaction was here investigated. The reaction of acetylated 2-deoxy-2-phthalimido-\(\beta\)-glucopyranosyl bromide (107) with allyltributyltin (2 mol. equiv.) and AIBN (0.3 mol. equiv.) in dry toluene at 85 \(^\circ\)C under Ar for 24 h gave the \(\beta\)-C-glycosylpropene 109 in 40\% yield. As expected, the stereospecific formation of a (2-amino-2-deoxy-\(\beta\)-\(\beta\)-glucopyranosyl)-1-propene derivative was achieved by choosing this large and rigid protecting group on 2-amino function. The large blocking group at C-2 decreased the rate of the free-radical reaction, and AIBN (0.15 mol. equiv., each time) was added to the solution twice. Purification on a column of silica gel provided 109 as a white solid, which could be crystallized from 3:1 hexanes-EtOAc to afford very beautiful needle crystals, mp 79–81 \(^\circ\)C, \([\alpha]\)\textsubscript{D} +70\(^\circ\) in chloroform. Exclusively the \(\beta\)-anomer was found by \(^1\)H-NMR spectra in the initial fractions. The \(^1\)H-NMR spectrum of 109 showed that the \(\beta\)-allyl C-glycosyl derivative 109 co-crystallized with the solvents ethyl acetate and hexanes in the ratio of 1 : 0.25 : 0.20 in the crystals. The solvents could not be removed under vacuum at room temperature, and the crystals were very stable in air. After drying with diminished pressure for 5 days, the ratio of 109 to solvents did not change. Eventually, the co-existing solvents were removed at 50 \(^\circ\)C under vacuum to leave a glassy solid, which was demonstrated to be pure 109 by the \(^1\)H-NMR spectrum and elemental analyses. A 1,2-elimination reaction was the major side-reaction in the preparation of 109, and led to the glycal 110 in 16\% yield. Because the elimination reaction produced HBr in the
system, the acetylated 2-deoxy-2-phthalimido-β-D-glucopyranosyl radical also
abstracted hydrogen radical from HBr, leading to the anhydro alditol 111 in 8%
yield. The glycal 110 and the glycitol 111 had the same R_{F} values.
Recrystallization gave the pure white crystalline 110, having mp 126–127 °C
and [α]_{D} -11° in chloroform. Ogawa et al. reported 110 as a syrup and [α]_{D}
-150.95 A pure preparation of 111 could not be obtained.
The β-anomeric configuration of 109 was assigned on the basis of \textsuperscript{1}H-
NMR data for H-2', which resonated as a triplet at δ 4.45 and showed J_{4';2'} 10.1
Hz. The large values of J_{2';3'}, J_{3';4'} and J_{4';5'} (9.9, 9.3, and 10.0 Hz) were in
accordance with the \textsuperscript{4}C_{1} D-glycopyranosyl chair conformation. The β-C-glycosyl
propene 109 showed an abnormal dextrorotatory ([α]_{D} +70° in chloroform).
Such rotatory anomalies are known in glycosides having certain aryl groups at
C-2.
The acetylated 2-acetamido-2-deoxy-α-D-glucopyranosyl chloride 92
reacted with allyltributyltin in the presence of AIBN produced the allylated
product 95 in 67% yield. However, the acetylated 2-deoxy-2-phthalimido-β-D-
glucopyranosyl chloride 108 did not give any allylation product under the same
free-radical allylation conditions. It appears that formation of the glycosyl
radical is influenced not only by the activating group at the anomeric center, but
also by the substituent group at the C-2 position.
In the free-radical allylation reaction of 2-amino-2-deoxy-D-
glucopyranosyl derivatives with allyltributyltin initiated by AIBN in toluene
solvent, the protecting groups on the 2-amino function and substituents at the
anomeric center evidently exert a large influence on stereoselectivity and the
course of the free-radical reaction. 2-Amino-2-deoxy-D-glucopyranosyl
derivatives with acetyl, trifluoroacetyl and p-methoxybenzylidene protecting
groups on the amino function favored formation of $\alpha$-allylation products during the free-radical reaction. The $N$-$p$-methoxybenzyldiene protected derivative gave exclusively the $\alpha$-product. The $\alpha$:$\beta$ stereoselectivity for the $N$-acetyl protecting group was 34:1, and 11:1 for the $N$-trifluoroacetyl protected derivative. The 2-phthalimido-2-deoxy-$D$-glucopyranosyl derivative gave exclusively the $\beta$-allylation product. The final steric outcome was not influenced by the configuration of activating substituents at the anomeric center. For 2-acetamido-2-deoxy-$D$-glucopyranosyl derivatives, both the $\alpha$-substituted chloride derivative 92 and $\beta$-substituted xanthate derivative 97 gave preponderantly the $\alpha$-allylation products. The substituent group at the anomeric center influenced the rate of free radical reaction. It is easier to break the C-Br bond than the C-Cl bond to produce the glucopyranosyl radical. It took 6 h for the bromide derivative 104 to complete the free-radical reaction, whereas, for the chloride derivative 92 it took 8 h, and overnight for the xanthate derivative 97. The protecting group on 2-amino function also influenced the free-radical reaction rate. For the 2-phthalimido-2-deoxy-$D$-glucopyranosyl derivative 107, AIBN needed to be added to the reaction system twice, and it took 24 h to consume all of the starting material.

The stereoselectivity in reactions of glycosyl radicals should be controlled by both stereoelectronic and steric effects. According to the ESR studies of Giese,$^{30,35,36}$ the glycosyl radicals may exist partially in the $B_{2,5}$ boat conformation, which would be stabilized by interaction of the SOMO in the radical with the LUMO of the neighboring carbon-oxygen bond. The interaction of the semioccupied orbital with the oxygen lone-pair of the ring oxygen make the SOMO–LUMO stabilization more significant. Some fraction of the glycosyl radical may adopt the $4C_1$ chair conformation of its precursor. In this situation,
the stereoelectronic effect is not large enough to compensate for the increase of steric strain in the course of the chair boat interconversion. Giese did not give a general rule for the tendency of glycosyl radicals to adopt either the $B_{2,5}$ boat conformation or the $^{4}C_1$ chair conformation. For glycosyl radical 29, when

$$\begin{align*}
29a & \\
29b &
\end{align*}$$

$X = \text{OAc, OMe and F}$, the radical appeared to exist in the distorted $B_{2,5}$ boat conformation, whereas the $^{4}C_1$ chair conformation was observed when $X = \text{NHTos, D, and C}_3\text{H}_7$. Fundamentally, glycosyl radicals are π-radicals and the unpaired electron occupies an orbital that has mainly $p$-character. The stereoelectronic effect makes attack from the $\alpha$-face to the glycosyl radical in the $^{4}C_1$ chair conformation more favorable because of the maintenance of interaction between the unpaired electron in the radical and the lone pair electrons on the ring oxygen in the transition state, and the $\alpha$-product is obtained exclusively. The stereoselectivity is relatively low for glycosyl radicals in the $B_{2,5}$ boat conformation, even though they favor $\alpha$-attack because of stereoelectronic effect. $\beta$-Attack is more favored for a glycosyl radical in the $^{1,4}B$ boat conformation. There is only a small energy difference between the $B_{2,5}$ boat and the $^{1,4}B$ boat, and this would account for the low stereoselectivity.
Direct ESR investigation of 2-amino-2-deoxy-D-glucopyranosyl radicals was not pursued at this time. Based on Giese's results, it was concluded that the acetylated 2-deoxy-2-p-methoxybenzylideneamino-D-glucopyranosyl radical should adopt the $^4C_1$ chair conformation because of the steric stain caused by the large protecting group, and lead exclusively to the $\alpha$-allylation product in the free-radical allylation reaction. The acetylated 2-acetamido-2-deoxy-D-glucopyranosyl and 2-trifluoroacetamido-2-deoxy-D-glucopyranosyl radicals should exist in the $B_{2,5}$ boat conformation and lead to an $\alpha$ and $\beta$ mixture of products with the $\alpha$-product being preponderant. The energy barrier between the $B_{2,5}$ and $^{1,4}B$ boat conformations in the 2-trifluoroacetamido-2-deoxy-D-glucopyranosyl radical should be much lower than that in the 2-acetamido-2-deoxy-D-glucopyranosyl radical because the latter gave much higher stereoselectivity ($\alpha:\beta = 34:1$) than the former ($\alpha:\beta = 11:1$) during the free-radical allylation reactions. It is believed that the acetylated 2-phthalimido-2-deoxy-D-glucopyranosyl radical adopts the $^4C_1$ chair conformation, and the observed complete $\beta$-selectivity was attributable mainly to the steric effect. $\alpha$-Attack was totally blocked by the rigid 2-phthalimido protecting group and exclusively the $\beta$-allylation product was formed.

The NMR data of allylation products 95, 98, 102, 102a, 105 and 109 are summarized in Tables 6—8. For the (2-amino-2-deoxy-$\alpha$-D-glucopyranosyl)propene derivatives 95, 98, 102, 102a and 105, the $^3J$ coupling constants of the hydrogens from the tetrahydropyran ring were smaller than those for the regular $^4C_1$ chair conformation. The larger and more polar the protecting group on the 2-amino function was, the smaller were the observed coupling constants. For $3$-(3,4,6-tri-$O$-acetyl-2-amino-2-deoxy-$\alpha$-D-glucopyranosyl)-1-propene (102a), there is no protecting group on the 2-amino
function, and the coupling constants were as follows: $J_{1',2'} = 5.3$ Hz, $J_{2',3'} = 9.4$ Hz, $J_{3',4'} = J_{4',5'} = 8.8$ Hz, and these are close to the normal coupling constants expected for the $4C_1$ conformation. For the propene derivative 105, the trifluoroacetyl protecting group on the 2-amino function was the largest and most polar among the investigated protecting groups for $\alpha$-products, and the observed coupling constants departed from normal value most severely ($J_{1',2'} = 3.8$ Hz, $J_{2',3'} = 6.0$ Hz, $J_{3',4'} = 5.8$ and $J_{4',5'} = 4.6$ Hz). The abnormal coupling constants suggested that the tetrahydropyran ring in the (2-amino-2-deoxy-$\alpha$-D-glucopyranosyl)propene derivatives is distorted from the $4C_1$ glycosyl chair conformation, or that the ring is in the rapid equilibrium between the $4C_1$ and $1C_4$ chair conformations, and the observed coupling constants were the weighted time-averages for the two chair conformers in rapid equilibrium. 3-(3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-$\beta$-D-glucopyranosyl)-1-propene (109) showed quite normal coupling constants for the $4C_1$ chair conformation ($J_{1',2'} = 10.2$ Hz, $J_{2',3'} = 10.2$ Hz, $J_{3',4'} = 9.0$ Hz, and $J_{4',5'} = 10.3$ Hz). In all of the 2-amino-2-deoxy-2-glucopyranosyl propenes obtained, the $J_{2',3'}$ value was larger than $J_{3',4'}$ and $J_{4',5'}$, and this may be attributed to the smaller electronegativity of the C–N bond at C-2 than the C–O bond.

The first-order $^1H$-$^1H$ coupling constants of 2-amino-2-deoxy-$\alpha$-D-glucopyranosyl halides 92, 100 and 104 are listed in Table 1. They are very close to the $^1H$-$^1H$ coupling constants expected for the normal $4C_1$ glycopyranosyl chair conformation. The strong anomic effect in the glycosyl halides leads compounds 92, 100, and 104 exist almost exclusively in the $4C_1$ chair conformation, no matter what kind of protecting groups is present on the 2-amino function.
Table 1. First-order $^1\text{H}-^1\text{H}$ coupling constants (Hz) of 2-amino-2-deoxy-$\alpha$-D-glucopyranosyl derivatives 92, 100 and 104.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$J_{1,2}$</th>
<th>$J_{2,3}$</th>
<th>$J_{3,4}$</th>
<th>$J_{4,5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
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<td>10.4</td>
<td>9.6</td>
<td>9.6</td>
</tr>
<tr>
<td>100</td>
<td>3.7</td>
<td>10.2</td>
<td>9.7</td>
<td>9.7</td>
</tr>
<tr>
<td>104</td>
<td>3.3</td>
<td>9.5</td>
<td>9.7</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Table 2. First-order $^1\text{H}-^1\text{H}$ coupling constants (Hz) of 1-C-$\alpha$-D-glucopyranosyl derivatives 1, 2 and 112.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$J_{1',2'}$</th>
<th>$J_{2',3'}$</th>
<th>$J_{3',4'}$</th>
<th>$J_{4',5'}$</th>
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<td>1</td>
<td>5.8</td>
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<td>9.0</td>
<td>9.0</td>
</tr>
<tr>
<td>2</td>
<td>5.5</td>
<td>9.2</td>
<td>9.2</td>
<td>9.2</td>
</tr>
<tr>
<td>112</td>
<td>5.3</td>
<td>8.5</td>
<td>8.5</td>
<td>8.5</td>
</tr>
</tbody>
</table>
The first-order $^1\text{H}-^1\text{H}$ coupling constants of $\alpha$-$\text{C-D}$-glucopyranosyl derivatives 1, 2 and 112 in Table 2 showed that the 1-C-allylated $\alpha$-$\text{D}$-glucopyranosides 1 and 2 adopted essentially the regular $^4C_1$ chair conformation, while the conformation of 112 was slightly distorted or in a rapid equilibrium between the $^4C_1$ and $^1C_4$ conformers, but the $^4C_1$ conformer was largely preponderant. At the conformational equilibrium, various conformers will be populated to extents depending on their relative free-energy content, according to the classical thermodynamic distribution. The relative free-energy content of a particular conformer is determined by a combination of the following factors: (1) steric interactions, (2) bond torsional strain, (3) bond angle strain, (4) electronic factors involving interaction of dipoles, and (5) the effects of solvation and hydrogen bonding. Experimental evidence, mainly from NMR spectroscopy, has suggested that most pyranoid sugars and their monocyclic derivatives exhibit a high degree of conformational homogeneity in one of the two chairlike conformations which are free from bond-angle strain and constitute potential-energy minima as compared with other theoretically possible conformations. Based on information derived from study of cyclohexane, steric analysis predicts that the most-stable conformation of pyranoses is a chair structure with bulky substituents in equatorial positions. Compared with carbocyclic systems, the oxygen-containing rings have shorter C-O bond and oxygen atom is smaller than carbon atom. These features will increase certain non-bonded repulsions. The orientation of a substituent on the anomeric center is, however, an exception, because at that position the anomeric effect — preference for the axial disposition of polar substituents, plays an important role. It is predictable that the $^4C_1$ chair conformation is
completely preponderant in 2-amino-2-deoxy-\(\beta\)-glucosyl halides 92, 100 and 104 due to both steric and anomeric effects. In C-glycosyl compounds, there is apparently no anomeric effect, and the most important factor for determining the stability of conformations is the steric effect. The predicted favored conformation for the \(\alpha\)-C-glycosylpropene derivatives 1, 2 and 112 should be the 4\(C_1\) chair conformation, which having three acetoxy group and one acytoxymethyl group oriented in equatorial position and an allyl groups in axial disposition.

Consideration of the "normal" coupling constants for the 4\(C_1\) chair conformation of the glycopyranose ring in 2-amino-2-deoxy-\(\alpha\)-\(\beta\)-glucopyranosyl derivatives and \(\alpha\)-C-\(\beta\)-glucopyranosyl derivatives suggests that the abnormal coupling constants for the 4\(C_1\) chair conformation from 1-C-allylated 2-amino-2-deoxy-\(\alpha\)-\(\beta\)-glucopyranoses were attributable to the amino function. With increasing of the protecting group's size and polarity, the coupling constants between hydrogens of the tetrahydropyran ring decreased, and the conformation of the tetrahydropyran ring departed more from the normal 4\(C_1\) chair conformation. The conformation was also influenced by the solvent. In a non-polar solvent such as deuterated benzene, the acetylated 2-trifluoroacetamido-2-deoxy-\(\alpha\)-\(\beta\)-glucopyranosyl propene 105 showed very abnormal coupling constants for the ring hydrogens (\(J_{1',2'}\) 3.8 Hz, \(J_{2',3'}\) 6.0 Hz, \(J_{3',4'}\) 5.8 and \(J_{4',5'}\) 4.6 Hz). In such polar solvents as deuterated acetone, the coupling constants of compound 105 increased dramatically (\(J_{1',2'}\) 4.9 Hz, \(J_{2',3'}\) 8.4 Hz, \(J_{3',4'} = J_{4',5'}\) 7.2 Hz). Variable-temperature \(^1\)H-NMR experiments were performed to gain further insight into the conformational behavior of the 2-amino-2-deoxy C-glycosyl derivatives. Spectra for compound 105 were recorded at temperatures ranging from 30 °C to -90 °C (Tables 3 and 4). A modest temperature effect was observed. With decrease of temperature, the chemical shifts of H-1b, H-3a,
Table 3. $^1$H-NMR chemical shifts ($\delta$) of compound 105 at different temperatures in acetone-$d_6$ at 500 MHz.

<table>
<thead>
<tr>
<th>Temp (K)</th>
<th>H-1'</th>
<th>H-2'</th>
<th>H-3'</th>
<th>H-4'</th>
<th>H-5'</th>
<th>H-6'</th>
<th>H-6'a</th>
<th>H-6'b</th>
</tr>
</thead>
<tbody>
<tr>
<td>303</td>
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<td>5.16</td>
<td>5.81</td>
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<td>2.39</td>
<td>4.22</td>
<td>4.32</td>
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<td>4.21</td>
<td>4.32</td>
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<tr>
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<td>4.35</td>
<td>5.28</td>
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<tr>
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<td>2.88</td>
<td>2.45</td>
<td>4.15</td>
<td>4.35</td>
<td>5.28</td>
</tr>
</tbody>
</table>

Table 4. Temperature dependence of the $^1$H-$^1$H coupling constants (Hz) of compound 105 in acetone-$d_6$ at 500 MHz.

<table>
<thead>
<tr>
<th>Temp.(K)</th>
<th>$J_{1',2'}$</th>
<th>$J_{2',3'}$</th>
<th>$J_{3',4'}$</th>
<th>$J_{4',5'}$</th>
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<tbody>
<tr>
<td>303'</td>
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</tr>
<tr>
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<tr>
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<tr>
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<td>5.0</td>
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</tr>
<tr>
<td>245</td>
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<td>5.0</td>
<td>10.2</td>
<td>9.1</td>
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</tr>
</tbody>
</table>

* At 500 MHz in C$_6$D$_6$. 
H-3b, H-2', and H-3' moved further downfield, and those of H-2, H-1', H-4', H-5', H-6'a and H-6'b moved upfield. All of the $^3J$ coupling constants for hydrogens of the tetrahydropyran ring increased. At 183 °K, the coupling constants reached their largest value and were close to the normal coupling constants for the $^4C_1$ chair conformation ($J_{1',2'} 5.0$ Hz, $J_{2',3'} 10.2$ Hz, $J_{3',4'} = J_{4',5'} 9.1$ Hz). The observation of a temperature effect indicated that compound 105 existed in equilibrium between the $^4C_1$ conformer 105b and $^1C_4$ conformer 105a as shown in Figure 3. The NMR-spectroscopic method of averaging of spin coupling can be used to determine the chair-chair conformational populations. The standard free-energy difference $\Delta G^\circ$ and equilibrium constant $K$ for the interconversion can be calculated from the following relationship:

$$\Delta G^\circ = -RT\ln K = -RT\ln \frac{N_a}{N_e}$$  (1)
where $N_a$ represents the mole fraction of the $^4C_1$ conformer 105b (H-2', H-3', H-4' and H-5' in axial position) and $N_e$ for the conformer 105a (H-2', H-3', H-4' and H-5' in equatorial position). The values of $N_a$ and $N_e$ are determined from the equation:

$$J_{\text{obs}} = N_e J_a + N_a J_e$$  \hspace{1cm} (2)

which relates a particular $^3J$ spin-coupling constant ($J_{\text{obs}}$) of a proton (one of H-2', H-3', H-4' and H-5') in question in the time-averaged spectrum with that ($J_a$) when the proton is exclusively axial in the $^4C_1$ conformation 105b and that ($J_e$) when it is exclusively equatorial in the $^1C_4$ conformation 105a.

The Karplus equation$^{98}$ has been used extensively in structural studies with pyranoid and furanoid sugar derivatives. The following equation:

$$J_{HH'} = A + B \cos \phi + C \cos 2\phi$$  \hspace{1cm} (3)

was derived from a valence-bond treatment of the dihedral-angle $\phi$ dependence of vicinal proton-couplings. Vicinal proton-couplings were found to depend not only on dihedral angle, but also on the electronegativity of substituents present, the C-C' bond length of the particular H-C-C'-H' unit under consideration, the bond angles and other molecular properties.$^{97}$ A better, semi-theoretical relationship is given in Karplus' later equation:

$$J_{HH'} = (A + B \cos \phi + C \cos 2\phi)(1 - \Delta \chi)$$  \hspace{1cm} (4)
where \( A, B, C, \) and \( m \) are constants, \( \phi \) is the dihedral angle, and \( \Delta X \) the difference in the electronegativities of the substituent and hydrogens.\(^\text{99}\)

Horton has made extensive investigations on the conformations of pyranoid sugar derivatives and has furnished accurate proton spin-spin coupling data for a broad range of peracylated D-aldopentopyranosyl derivatives,\(^\text{100}\) including three complete configurational series, the eight peracetylated aldopentopyranoses, the eight perbenzoylated aldopentopyranoses and the eight peracetylated methyl aldopentopyranosides. A reasonable set of empirical values to use in the generalized Karplus equation (4), which was expected to give satisfactory results for carbohydrates, was given by Horton\(^\text{100a}\) in the following expression:

\[
J_{HH'} = (7.8 - 1.0 \cos \phi + 5.6 \cos 2\phi) (1 - 0.1 \sum \Delta X)
\]  
(5)

which was used to calculate theoretical \( ^3J_{HH'} \) values for the various \( H-C-C'-H' \) units, assuming ideal ring-geometry.

For 3-(3,4,6-tri-O-acetyl-2-deoxy-2-acetamido-\( \alpha \)-D-glucopyranosyl)-1-propene (105), the vicinal coupling constant between \( H-3' \) and \( H-4' \) \( (J_{3',4'}) \) was chosen to evaluate the conformational equilibrium. At \(-90 \, ^\circ C\), the vicinal coupling constants of hydrogens of the tetrahydropyran ring reached their largest values. It was considered that the \( ^4C_1 \) conformer 105b was present in the solution as essentially the exclusive form, and \( J_{3',4'} = 9.1 \, Hz \) at \(-90 \, ^\circ C\) was chosen as \( J_{3',4'} \). The value of \( J_{3',4'} \) was calculated according to the equation (5) assuming ideal ring-geometry \( (\phi_{ee} = 60^\circ) \) and the electronegativity for the OAc substituent as 3.72, to give \( J_{3',4'} = 2.68 \, Hz \). The calculated conformer populations of 105b, the equilibrium constant \( K \), and the free-energy
difference $\Delta G^0$ at different temperatures are listed in Table 5. At 30 °C, the $1C_4$ conformer 105a was somewhat favored in benzene solution ($N_a = 0.51$), whereas the $4C_1$ conformer 105b was preponderant at equilibrium in acetone solvent ($N_a = 0.70$). With decreasing temperature a progressive shift in the conformational equilibrium toward exclusive favoring of the $4C_1$ conformation was detected by an increase in the coupling constants and reflected by the increased equilibrium constant $K$ and decreased free-energy difference.

Table 5. Temperature dependence of $J_{3',4'}$, equilibrium constant $K$ and free-energy difference $\Delta G^0$ of compound 105 in acetone-$d_6$.

<table>
<thead>
<tr>
<th>Temp.(K)</th>
<th>$J_{3',4'}$</th>
<th>$N_a$</th>
<th>$K$</th>
<th>$\Delta G^0$ (kcal mole$^{-1}$)</th>
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<td>-0.82</td>
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<tr>
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</tr>
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<tr>
<td>213</td>
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<tr>
<td>183</td>
<td>9.1</td>
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<td>&gt;50</td>
<td>&lt;-1.42</td>
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</table>

* At 500 MHz in C$_6$D$_6$.

In the non polar solvent, conformer 105a ($1C_4$) was somewhat more favored than conformer 105b ($4C_1$) (105a:105b = 51:49). Based on steric effects, conformer 105b should be much more favored, because there are two acetoxyl groups, one trifluoroacetamido group and one acetoxymethyl group in equatorial positions and only one group allyl is in axial disposition. In conformer 105a, all of the substituents are in axial disposition except the allyl
group at C-1', which is in equatorial disposition. A strong non-bonded interaction should exist in conformer 105a. The hydrogen atom on the amino function may play an important role in the stabilization of the steric unfavored conformer 105a ($^1C_4$). This hydrogen could form an intramolecular hydrogen bonding with the ring oxygen in conformer 105a, and this should help significantly stabilizing the $^1C_4$ conformation. This hypothesis of intramolecular hydrogen bonding is supported by the fact that the $^1C_4$ and $^4C_1$ conformational equilibrium is strongly influenced by solvents. In a nonpolar solvent such as benzene, the intramolecular hydrogen bonding was very strong and the conformer 105a was favored, with an equilibrium constant $K = 0.95$. When the solvent was changed to a polar solvent such as acetone, the intermolecular hydrogen bonding with solvent competed with the intramolecular hydrogen bonding, and the conformer 105b was more favored and the equilibrium constant $K$ increased to 2.38. The protecting group on the amino function should influence the ability of amino hydrogen to engage in hydrogen bonding. A strongly electron-withdrawing protecting group will facilitate the amino hydrogen atom to engage in hydrogen bonding. If the same parameters as for
105 ($J_{3'e,4'e} = 2.68$ Hz and $J_{3'a,4'a} = 9.1$ Hz) are used to calculate the conformational population of 95 in deuterated benzene solvent at $30$ °C, the results is that $N_a = 0.64$, $K = 1.79$ and $\Delta G^0 = -0.351$ kcal mol$^{-1}$. In compound 95, the acetyl protecting group on the amino function is less polar than the trifluoroacetyl protecting group in compound 105, and the intramolecular hydrogen bonding is not as strong as that in 105a. As a result, the population of the $^4C_1$ conformer in 95 increased to 64% as compared with 49% in 105 under the same conditions. There was no intramolecular hydrogen bonding evident in the non-aminated $\alpha$-C-glucopyranosylpropene analogues 1, 2 and 112, and the $^4C_1$ chair conformation was the exclusive conformer. This observation also supports the hypothesis of intramolecular hydrogen bonding existing in the 2-amino-2-deoxy-$\alpha$-C-glucopyranosylpropenes. Although intramolecular hydrogen bonding would be possible in the $^1C_4$ conformers of the 2-amino-2-deoxy-$\alpha$-D-glucopyranosyl halides 92, 100 and 104, the strong anomeric effect outweighs such hydrogen bonding and makes the $^4C_1$ conformation the exclusive form in solution.

2. Allylation of 2-amino-2-deoxy-galacto and mannopyranosyl derivatives via a free-radical reaction

The foregoing results show that the allyl group can be successfully introduced at C-1' of 2-amino-2-deoxy-D-glucopyranose derivatives through a free-radical reaction using allyltributyltin, with resonable yield and short steps. The generality of this methodology was further evaluated with 2-amino-2-deoxy-D-galactopyranose and 2-amino-2-deoxy-D-mannopyranose.
Preparation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl chloride (115). Compound 115 was prepared by two different methods. Starting from D-galactosamine hydrochloride, 2-acetamido-2-deoxy-D-galactopyranose was prepared in quantitative yield by Horton's procedure\cite{84} for gluco analogue. This was then treated with acetyl chloride. This gave a mixture of the desired chloride 115 (29%) along with 2-methyl-(2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-galactopyran)-[2,1-d]-2-oxazoline (116) in the ratio of 1:0.85. In the gluco series, this procedure leads exclusively to the chloride. Acetylation of D-galactosamine hydrochloride in
pyridine and acetic anhydride\textsuperscript{101} produced the corresponding $\alpha,\beta$-pentaacetate (114) in total 68\% yield, which could be resolved to give pure $\alpha$ product, pure $\beta$ product and $\alpha,\beta$ mixed products. The pure $\beta$-anomer of 114 reacted with TiCl$_4$ to give the pure chloride 115 in 88\% yield, while $\alpha,\beta$ mixture of 114 provided a mixture of chloride 115 (66\%) and oxazoline 116 in the ratio of 4:1 under the same reaction conditions.

**Free-radical allylation reaction of compound 115:** Synthesis of 3-(2-acetamido-3,4,6-tri-$O$-acyetyl-2-deoxy-$\alpha$-D-galactopyranosyl)-1-propene (117). Compound 117 was synthesized by the reaction of acetylated 2-acetamido-2-deoxy-$\alpha$-D-galactopyranosyl chloride (115) with allyltributyltin and AIBN in dry toluene for 7 h at 85 °C under Ar. As it proved difficult to obtain pure 115 for the free-radical reaction through the reaction of 2-acetamido-2-deoxy-D-galactopyranose with acetyl chloride, the mixture of 115 and oxazoline 116 was used without further separation and purification because of the easy conversion of chloride 115 into oxazoline 116. The yield was calculated on the basis of the chloride 115 present. After work-up with acidic acetone (to decompose the oxazoline 116, which had an $R_F$ value very close to that of the product 117) and purification on a column of silica gel, 117 was obtained in 56\% yield as a white solid that crystallized from 2:1 hexanes–EtOAc to afford needles, mp 129–130 °C; [$\alpha$]$D^\circ$ +81° in chloroform. The $\alpha$-anomeric configuration of 117 was confirmed by the coupling constant value of $J_{1',2'}$ 4.8 Hz. The normal coupling constants of hydrogens from tetrahydropyran ring ($J_{1',2'}$ 4.8 Hz, $J_{2',3'}$ 9.4 Hz and $J_{3',4'} = J_{4',5'}$ 3.2 Hz) indicates that 117 adopts the $^4C_1$ conformation in the solution.

When the compound 115 that was prepared from the reaction of galactosamine pentaacetate (114) with TiCl$_4$, was used for the free-radical
reaction under the same reaction conditions, the allylated product 117 could not be detected, only oxazoline 116 and the polymerization product were found. It was believed that a trace amount of TiCl₄ was present in the starting material, which would catalyze the conversion of 115 to 116 and also polymerize the allylated product.

Scheme 36

Preparation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-mannopyranosyl chloride (119). Compound 119 was prepared following the traditional method of Baker. α-D-Mannosamine pentaacetate (118) was prepared from D-mannosamine hydrochloride in pyridine and acetic anhydride solution. Chlorination of compound 118 at the anomeric center in acetic acid with anhydrous HCl gave compound 119 in 53% yield.
Free-radical allylation reaction of compound 119: Formation of 2-methyl-(2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-β-D- mannopyranosyl)-(2,1-d)-2-oxazoline (120). The reaction of 2-acetamido-2-deoxy-α-D-mannopyranosyl chloride with allyltributyltin (3 mol. equiv.) and AIBN (0.15 mol. equiv.) in dry toluene did not give the desired allylation product, and instead the oxazoline 120 was obtained in 82% yield, mp 127-128 °C (from ether), [α]_D -31° in chloroform; lit.103 mp 132-133 °C; [α]_D -30°. With D-mannosamine, the neighboring-group participation effect is much stronger than with D-glucosamine and D-galactosamine, and the 1,2-ring-closure reaction is evidently much faster than the free-radical reaction, and so only the neighboring-group participating product, oxazoline 120, was formed when the acetyl protecting group was used on the amino function.

3. Allylation of glucopyranosyl derivatives via an allylsilyl method

Preparation of 2,3,4,6-tetra-O-benzyl-1-O-p-nitrobenzoyl-β-D-
glucopyranose (123). Compound 123 was prepared by a modification of the procedure of Glaudemans and Fletcher.104 Methyl α-D-glucopyranoside was treated with benzyl chloride in the presence of potassium hydroxide in 1,4-dioxane solution to provide the benzylated methyl glucopyranoside intermediate 121 as a syrup, which was not purified and was subjected directly to acidic hydrolysis. The intermediate 121 was hydrolyzed in acetic acid and 1 M H_2SO_4 at 75-80 °C to give 2,3,4,6-tetra-O-benzyl- α-D-glucose (122) having mp 152-153 °C and [α]_D +16.0° in 62% yield. It was quite important to control the hydrolysis temperature to assure a high yield. If the temperature was below
75 °C, compound 121 would not dissolve completely in acetic acid, and if the temperature was too high, a mixture of α and β-anomers of 122 was obtained. Compound 122 reacted with p-nitrobenzoyl chloride in the presence of pyridine in dichloromethane solution at room temperature to afford the activated glucose derivative 123 in 91% yield as a mixture of α and β-anomers in the ratio of 1.00:2.73. The pure α and β-anomers of 123 could be obtained by repeated recrystallization from diisopropyl ether.

Preparation of 3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-propene (124). The 1-C-allylated compound 124 was synthesized by a
modification of the reaction conditions of Horton and coworkers.\textsuperscript{21a,b} The activated D-glucopyranose 123 (α:β 1.00:2.73) was allylated at the anomeric center by reaction with allyltrimethylsilane, using boron trifluoride etherate as catalyst in acetonitrile at low temperature to give compound 124 in 92\% yield with a stereoselectivity of α:β 98:2. This high yield and high stereoselectivity could be achieved when the reaction conditions were controlled carefully. It is established that low temperature favors the α-product. The function of Lewis acid, BF\textsubscript{3}-OEt\textsubscript{2}, is to promote the departure of the 1-substituent and produce an oxonium intermediate for attack of the nucleophile. If the catalyst would be added to the reaction system all at once, a large amount of oxonium ion would be rapidly produced and then the chance of β-attack would be increased and lead to low stereoselectivity. It was found better to add boron trifluoride etherate slowly to the system concurrently with the nucleophilic reagent allyltrimethylsilane, which then captures the newly formed oxonium ion immediately via the stereoelectronically preferred axial addition mode. The experimental results demonstrated that the concentrated solution gave higher stereoselectivity than a dilute solution. In concentrated solution, the nucleophile attacks the oxonium ion more rapidly. The stereoselectivity was not influenced by the stereochemistry of the substituent at the anomeric center of the starting material. But it was observed by TLC that the β-anomer of 123 was more reactive than the α-anomer. After 2.5 h at 0 °C, all of the β-anomer of 123 had all been consumed, but the spot for the α-anomer on TLC disappeared only during overnight reaction at room temperature. When compound 123 forms a complex with the Lewis acid BF\textsubscript{3}-OEt\textsubscript{2} at the O-1 position, the oxygen atom linked to the anomeric center becomes positively charged. According to the reverse anomeric effect,\textsuperscript{106} this β-complex would be stable and thus more
readily formed, which explains why the β-anomer of 123 reacts much faster than the α-anomer in the nucleophilic allylation reaction.

In general, the reaction course and stereoselectivity of C-allylation at the anomeric center of sugars, having non-participating groups at C-2, with allylsilane reagents in the presence of a Lewis acid catalyst are influenced by the substituent group at the anomeric center, the solvent, the reaction temperature and the nature of the Lewis acid. It is considered that the mechanism for the allylsilane nucleophilic addition reaction is first to produce the open oxonium ion 125. This oxonium ion should preferentially accept nucleophiles from the α (axial) side because of the anomeric effect from the ring oxygen. The substituent group at the anomeric center has a great impact on the rate of production of the oxonium ion 125, but not on the stereoselectivity.

2,3,4,6-Tetra-O-benzyl-D-glucopyranose reacted with allyltrimethylsilane and boron trifluoride etherate in acetonitrile at room temperature to yield a 10:1 mixture of 124 and its β-anomer in 55% combined yield. The chemical yield of the coupling reaction was improved to 80% with the same stereoselectivity, by using the activated glucosyl derivative 123. Solvents exert a large influence on the stereoselectivity. When β-D-glucose pentaacetate was
allylated at C-1 with allyltrimethylsilane and BF$_3$·OEt$_2$ in dichloroethane as solvent, about equimolar quantities of the $\alpha$ and $\beta$-products were obtained.$^{21e}$ Conducting the reaction in acetonitrile produced a selective abundance (up to 95%) of the $\alpha$-allylation product.$^{21e}$ The conformational equilibrium between the oxonium ion conformers 127a and 127b should be markedly influenced by solvents. The oxonium ion 127a would favor production of the $\alpha$-product and 127b the $\beta$-product because of the anomeric effect from the ring oxygen. In such less-polar solvents as 1,2-dichloroethane, the energy barrier between the two conformers 127a and 127b may not be large enough to make one oxonium ion conformation preponderant in the reaction system. As a result, about equimolar amounts of $\alpha$ and $\beta$-products are produced. In such polar solvents as acetonitrile, the oxonium ion conformer 127a will be much more favored than conformer 127b, this would lead selectively to the $\alpha$-product. The ability of different Lewis acids to produce the oxonium ion intermediate is different. BF$_3$·OEt$_2$ is much more powerful than ZnX$_2$. BF$_3$·OEt$_2$ usually catalyzed the allylation reaction at the anomeric center of activated glycosyl derivatives at 0 °C–room temperature whereas ZnX$_2$ requires an elevated temperature.$^{21d}$ Trimethylsilyl trifluoromethanesulfonate and iodo(trimethyl)silane have also been used effectively as catalysts to promote the nucleophilic allylation reaction at the anomeric center of sugars.$^{21g}$
Figure 4. The mechanism for the formation of α and β nucleophilic addition products at the anomeric center.
Table 6. $^1$H-NMR chemical shifts (δ) and multiplicities of compounds 95$^a$, 102$^b$, 102$^a$, 105$^c$, 109$^a$ and 117$^a$.

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<tr>
<th>Compd</th>
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<th>H-1b</th>
<th>H-2</th>
<th>H-3a</th>
<th>H-3b</th>
<th>H-1'</th>
<th>H-2'</th>
<th>H-3'</th>
<th>H-4'</th>
<th>H-5'</th>
<th>H-6'a</th>
<th>H-6'b</th>
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$^a$At 300 MHz in C$_6$D$_6$. $^b$At 300 MHz in CDC$_3$. $^c$At 500 MHz in C$_6$D$_6$. 


Table 7. The first-order $^1$H-$^1$H coupling constants (Hz) of compounds 95$^a$, 102$^b$, 102$^a$, 105$^c$, 109$^a$ and 117$^a$.

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<th>Compound</th>
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<th>$J_{1b,2}$</th>
<th>$J_{1a,3a}$</th>
<th>$J_{1b,3a}$</th>
<th>$J_{1a,3b}$</th>
<th>$J_{1b,3b}$</th>
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$^a$At 300 MHz in C$_6$D$_6$. $^b$At 300 MHz in CDCl$_3$. $^c$At 500 MHz in C$_6$D$_6$. 
Table 8. $^{13}$C-NMR chemical shifts (δ) of compounds 95$^a$, 102$^b$, 102$^a$, 105$^c$, 109$^c$ and 117$^d$.

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$^a$At 63 MHz in CDCl$_3$. $^b$At 75 MHz in CD$_3$OD. $^c$At 75 MHz in C$_6$D$_6$. $^d$At 75 MHz in CDCl$_3$. 
Figure 5. $^1$H-NMR spectrum of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-\textalpha-D-glucopyranosyl)-1-propene (95)
Figure 6. $^{13}$C-NMR spectrum of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-$\alpha$-D-glucopyranosyl)-1-propene (95)
Figure 7. $^1$H-NMR spectrum of 3-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-1-propene (98)
Figure 8. $^{13}$C-NMR spectrum of 3-(2-acetamido-2-deoxy-$\alpha$-D-glucopyranosyl)-1-propene (98)
Figure 9. $^1$H-NMR spectrum of 3-(2-acetamido-6-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (98a)
Figure 10. $^{13}$C-NMR spectrum of 3-(2-acetamido-6-O-acetyl-2-deoxy-$\alpha$-D-glucopyranosyl)-1-propene (98a)
Figure 11. $^1$H-NMR spectrum of 3-(3,4,6-tri-O-acetyl-2-amino-2-deoxy-$\alpha$-D-glucopyranosyl)-1-propene hydrochloride (102)
Figure 12. $^{13}\text{C}$-NMR spectrum of 3-(3,4,6-tri-O-acetyl-2-amino-2-deoxy-$\alpha$-d-glucopyranosyl)-1-propene hydrochloride (102)
Figure 13. $^1$H-NMR spectrum of 3-(3,4,6-tri-O-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl)-1-propene (102a)
Figure 14. $^{13}$C-NMR spectrum of 3-(3,4,6-tri-O-acetyl-2-amino-2-deoxy-\(\alpha\)-D-glucopyranosyl)-1-propene (102a)
Figure 15. $^1$H-NMR spectrum of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-
trifluoroacetamido-α-D-glucopyranosyl)-1-propene (105)
Figure 16. $^{13}$C-NMR spectrum of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)-1-propene (105)
Figure 17. $^1$H-NMR spectrum of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-$\beta$-d-glucopyranosyl)-1-propene (109)
Figure 18. $^{13}$C-NMR spectrum of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-$\beta$-D-glucopyranosyl)-1-propene (109)
Figure 19. $^1$H-NMR spectrum of 2-acetamido-3,4,6-tri-O-acetyl-α-D-galactopyranosyl chloride (115)
Figure 20. $^{13}$C-NMR spectrum of 2-acetamido-3,4,6-tri-O-acetyl-$\alpha$-D-galactopyranosyl chloride (115)
Figure 21. $^1$H-NMR spectrum of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-$\alpha$-$\delta$-galactopyranosyl)-1-propene (117)
Figure 22. $^{13}$C-NMR spectrum of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl)-1-propene (117)
Figure 23. \(^1\text{H-NMR}\) spectrum of 3-(2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-glucopyranosyl)-1-propene (124)
Figure 24. $^{13}$C-NMR spectrum of 3-(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-1-propene (124)
B. Synthesis of C-linked Glycosylalkenes and C-Linked Glycosylalkadienes

Ozonolysis of 3-(α-D-glucopyranosyl)-1-propene: Synthesis of 2-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)ethanal (130), 2-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)ethanal (131), and 2-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)ethanal (132). The allyl group is a good precursor for further functionalization. The most common methodology for such functionalization is oxidative cleavage of the alkene to produce an aldehyde or carboxylic acid. Of the more selective oxidants, ozone is perhaps the most widely used for carbon–carbon double bond cleavage. Ozonolysis has the added advantage that, by suitable choice of the method of work-up, the oxidation may yield carbonyl compounds, alcohols, or carboxylic acids. Oxidation of alkenes leading to aldehydic fragments may also be performed by the combination of osmium tetroxide–sodium metaperiodate (Lemieux–Johnson reagent). Cleavage of alkenes to ketones and carboxylic acid is conveniently performed by using the combination of potassium permanganate–sodium metaperiodate (Lemieux–von Rudloff reagent) or ruthenium tetroxide–sodium metaperiodate. Reaction of an alkene with ozone in an inert solvent usually affords an ozonide, which may, without isolation, be reduced with a variety of reagents to give a mixture of carbonyl compounds. The reaction is attractive for synthetic purposes because of the quantitative cleavage of a carbon–carbon double bond under very mild conditions in most cases. The mechanism of formation of ozonide 129 is thought to involve three steps (Figure 25), all of which are 1,3-dipolar reactions. In step a, ozone
adds as a 1,3-dipole in a stereospecific manner to afford the primary ozonide, which is thermally unstable and decomposes (step b) even at low temperature into a carbonyl compound and a carbonyl oxide. The latter is an energy-rich species and most frequently combines (step c) with the aldehyde or ketone fragment to give ozonide 129. In the presence of an alcohol, addition of alcohol to the carbonyl oxide may take place to give a geminal alkoxyhydroperoxide. Ozonolysis is usually performed at low temperature and inert solvents such as hexane, carbon tetrachloride, N, N-dimethylformamide, methanol, ethanol, water, or acetic acid. Generally, the direct products of ozonization are not isolated, but are decomposed by hydrolysis, reduction, or oxidation.
The ozonolysis of benzylated 3-(α-D-glucopyranosyl)-1-propene (124) in the presence of 1.5 molar equivalents of methanol in dichloromethane solvent at -77 °C provided the C-linked glycosyl aldehyde 130 as a syrup in 83% yield after reduction with dimethyl sulfide. The 1H-NMR spectrum of the product clearly showed the aldehyde hydrogen peak at δ 9.72 as a doubled doublet, but the aldehyde 130 did not exist as a single molecular entity and the integration of the aldehyde hydrogen peak was smaller than one unit. The product 130 was used in the next reaction without further purification. The purpose of using 1.5 molar equivalents of methanol was to accelerate reduction of the intermediate ozonide to the aldehyde by dimethyl sulfide. Without methanol, more than a week was required for the complete reduction. If more than 2 molar equivalent of methanol was used, a side product having an RF value a little higher than that of compound 130, possibly the aldehyde dimethyl acetal, increased.

The ozonolysis of the N-substituted 2-amino-2-deoxy-α-D-glucopyranosylpropenes 95 and 105 in dichloromethane solvent at -77 °C
with subsequent reduction by dimethyl sulfide gave the corresponding aldehyde products 131 in 75% yield and 132 in 84% yield, respectively. Both aldehyde products 131 and 132 were obtained as syrups and were used directly without further purification. For the ozonolysis of protected 2-amino-2-deoxy glycopyranosylpropanes, methanol could not be used to accelerate the rate of reduction as it led to a large proportion of side products. Reduction of the intermediate ozonide from compound 95 took more than three days, but only one day was required for reduction of the ozonide from compound 105. The \(^1\text{H}\)-NMR and MS data demonstrated that the products were the desired C-glycosylaldehydes 131 and 132.

Wittig reaction of C-linked α-D-glycopyranosylaldehydes with methyl (triphenylphosphoranylidene)acetate: Synthesis of methyl (E)-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-but-2-enoate (133), methyl (E)-4-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-but-2-enoate (134), and methyl (E)-4-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)-but-2-enoate (135). The conventional Wittig reaction entails the reaction of a phosphonium ylid with an aldehyde or a ketone. The net result is the carbonyl group is replaced by an ethylene unit. The Wittig reaction has enjoyed widespread prominence and recognition because of its simplicity, efficiency and effective stereocontrol. High selectivity for both (Z)- or (E)-alkenes is available, depending on the particular circumstances, such as the type of ylid, type of carbonyl compound, and the reaction conditions. Phosphorus ylids have been classified according to their general reactivity. "Stabilized" ylids that have strongly conjugating substituents (e.g. COOMe, CN or SO\(_2\)Ph) on the ylidic
carbon usually favor the production of (E)-alkenes. "Semistabilized" ylides with mildly conjugating substituents (e.g. Ph, or allyl) give no great preference one way or the other. "Non stabilized" ylides that lack such functionalities usually favor (Z)-alkenes.112

\[ \text{RO} \quad \text{Ph}_3\text{PCHCO}_2\text{CH}_3 \quad \text{H} \quad \text{Ph}_3\text{PCHCO}_2\text{CH}_3 \quad \text{Ph}_3\text{PCHCO}_2\text{CH}_3 \]

Scheme 39

The Wittig olefination reaction was chosen to approach the functionalized sugar alkenes as dienophiles from sugar-derived aldehydes for Diels–Alder cycloaddition studies. The benzylated \( \alpha \)-D-glucopyranosyl aldehyde 130 reacted with 2 equivalent of Wittig reagent methyl (triphenylphosphoranylidene)acetate in refluxing benzene for 24 h to provide methyl (E)-\( \alpha \)-(2,3,4,6-tetra-O-benzyl-\( \alpha \)-D-glucopyranosyl)-but-2-enoate (133) in 94% yield. The cis-isomer of 133 was also found in 3.3% yield. The total ratio of trans- and cis-products was 97:3. Crystalline needles of 133 having mp 60.0–61.5 °C and \([\alpha]_D^\circ +59.2^\circ\) in chloroform were obtained after recrystallization from 3:1 hexanes–ether. In the \( ^1\text{H}-\text{NMR} \) spectrum, a single methoxy peak was
observed at δ 3.71. The signals for H-2 and H-3 appeared at δ 5.91 as a doublet ($J_{2,3} = 15.7$ Hz) and δ 6.96 as a doubled triplet ($J_{3,4a} = J_{3,4b} = 7.2$ Hz, and $J_{2,3} = 15.7$ Hz), respectively. The signals for hydrogens at C-4 appeared in the upfield at δ 2.61 as multiplets. The large coupling constant of $J_{2,3} = 15.7$ Hz indicated that compound 133 was the trans-product. The $^{13}$C-NMR spectrum also verified that the correct product was obtained (δ 166.55 for CO$_2$CH$_3$, δ 145.38 for C-3, δ 122.95 for C-2, and δ 28.45 for C-4).

The acetylated 2-acetamido-2-deoxy-α-D-glucopyranosyl aldehyde 131 reacted with methyl (triphenylphosphoranylidene)acetate in refluxing benzene overnight to give the trans-α,β-unsaturated ester 134 in 59% total yield. It was found that the product 134 had the same Rf value (Rf 0.40, EtOAc) as the co-product triphenylphosphine oxide, and it was impossible to separate them directly. The mixture of 134 with triphenylphosphine oxide was dissolved in dry methanol and a catalytic amount of methoxide in methanol was added for deacetylation of compound 134. After neutralization of the solution with dry-ice and evaporation of methanol, triphenylphosphine oxide was removed completely by washing the residue with ethyl acetate repeatedly until a white solid was left. Reacetylation in pyridine and acetic anhydride, and recrystallization from 2:1 hexanes-EtOAc afforded compound 134 as needle crystals having mp 136-137 °C and $[\alpha]_D^{20} +69.0^\circ$ in chloroform. The trans-relationship in compound 134 was established through the observed large $J_{2,3}$ coupling constant of 15.7 Hz. The signal for H-3 was at δ 6.98 as a doubled triplet ($J_{3,4a} = J_{3,4b} = 7.0$ Hz, and $J_{2,3} = 15.7$ Hz), and H-2 at δ 5.91 as a doublet ($J_{2,3} = 15.7$ Hz). A single methoxy peak appeared at δ 3.69, and signals for H-4a and H-4b were observed at δ 2.51 and δ 2.37 as multiplets, respectively. In the $^{13}$C-NMR
spectrum of compound 134, C-3 appeared at $\delta$ 143.6, C-2 at $\delta$ 123.4, and C-4 at $\delta$ 30.8.

The Wittig reaction of acetylated 2-trifluoroacetamido-2-deoxy-\(\alpha\)-D-glucopyranosyl aldehyde 132 with methyl (triphenylphosphoranylidene)acetate in refluxing benzene for 7 h afforded the product 135 in 84% yield, obtained as white crystals having mp 122.5-123.5°C and $[\alpha]_D +31.1^\circ$ in chloroform after recrystallization from 10:3 hexanes–EtOAc. The large $J_{2,3}$ coupling constant of 15.7 Hz indicated that product 135 was the trans-isomer. In the $^1$H-NMR spectrum of compound 135, the signal for H-3 was located at $\delta$ 6.90 as a doubled triplet ($J_{3,4a} = J_{3,4b}$ 7.1 Hz, and $J_{2,3}$ 15.7 Hz), and H-2 at $\delta$ 5.95 as a doublet ($J_{2,3}$ 15.7 Hz). The upfield multiplets at $\delta$ 2.51 and $\delta$ 2.33 were attributed to H-4a and H-4b. In the $^{13}$C-NMR spectrum, the peaks at $\delta$ 142.78 and $\delta$ 123.86 indicated the presence of double bond from C-3 and C-2. The signal for C-4 appeared at $\delta$ 32.12.
Wittig reaction of C-linked α-ᴅ-ᴅ-glycosyl aldehyde 130 with 1-triphenylphosphoranylidene-2-propanone: Synthesis of (E)-5-(2,3,4,6-tetra-O-benzyl-α-ᴅ-glucopyranosyl)-pent-3-en-2-one (136). The C-linked α-ᴅ-glycopyranosyl aldehyde 130 reacted with the Wittig reagent 1-triphenylphosphoranylidene-2-propanone in refluxing benzene during 18 h to produce the trans-α,β-unsaturated methyl ketone product 136 in 79% yield. Compound 136 was recrystallized from 4:1 hexanes–ether to afford white crystals having mp 104–106 °C and [α]_D +57.8 °C in chloroform. The 3,4-trans-relationship was based on the large coupling constant of J$_{3,4}$ 16.0 Hz. In the $^1$H-NMR spectrum of compound 136, the signal for the methyl group appeared as a singlet at δ 2.15, H-3 as a doublet (J$_{3,4}$ 16.0 Hz) at δ 6.13, H-4 as a doubled triplet (J$_{3,4}$ 16.0 Hz, J$_{4,5a}$ = J$_{4,5b}$ 7.1 Hz) at δ 6.77, and H-5a and H-5b as multiplets at δ 2.64. In the $^{13}$C-NMR spectrum, the peak at δ 198.25 clearly indicated the presence of ketone carbonyl group in the molecule. The signals for C-1, C-3, C-4, and C-5 appeared at δ 26.52, 133.16, 144.19 and 28.79, respectively.
Wittig reaction of acetylated 2-acetamido-2-deoxy-α-D-glucopyranosyl aldehyde 131 with 1-triphenylphosphoranylidene-2-propanone: Synthesis of 4(R)-acetonyl-(2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyranosyl)-[3,2-b]-pyrrolidine (138). The treatment of 2-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)ethanal (131) with 1-triphenylphosphoranylidene-2-propanone in refluxing benzene did not give as expected the (E)-5-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-pent-3-en-2-one (137). The final product, obtained in 80% yield, was purified as a foamy solid exhibiting a large dextrorotation ([α]D +124.7° in chloroform). The product was identified as compound 138 by specific optical rotation, elemental analysis, NMR spectra and its mass spectrum. The elemental analysis and MS indicated that the product was either compound 137 or compound 138. Compounds 137 and 138 have the same molecular weight and elemental compositions, and it was
impossible to distinguish them through elemental analysis or mass spectrum. The $^1$H-NMR spectra of the product clearly showed the absence of signals for N-H and hydrogens connected with a double bond. Instead, there were two signals from hydrogens connected to C-3, at $\delta$ 3.47 as a doubled doublet ($J_{3\alpha,4} 3.1$ Hz and $J_{3\alpha,3b} 17.7$ Hz) and $\delta$ 2.57 as a doubled doublet ($J_{3b,4} 10.3$ Hz). If there were an $\alpha,\beta$-double bond, there would be only one hydrogen on C-3, and it should appear further downfield in the double-bond region. The peak for H-4 was observed at $\delta$ 4.35 as a multiplet. The signals for H-5a and H-5b were at $\delta$ 2.51 and $\delta$ 1.89 as multiplets, respectively. The $^{13}$C-NMR spectrum of compound 13B showed a single peak at $\delta$ 206.44, indicating the presence of a ketone carbonyl group, but there were no signals between $\delta$ 120–150 ppm for the carbons of a double bond. Both the $^1$H- and $^{13}$C-NMR spectra were consistent with the assigned structure of compound 13B. The stereochemistry at C-4 in compound 13B was determined according to the observed NOE effect.

![Diagram of compound 13B](image)

Figure 26. The NOE enhancement of compound 13B
The large NOE (in CD$_3$Cl) increase at H-4 (12.15%) when H-1' was irradiated indicated that H-4 and H-1' were in cis-relationship, and as a result, C-4 was in the $R$ configuration. It is considered that compound 138 is produced through 1,4-Michael addition reaction of the acetamido group to the $\alpha,\beta$-unsaturated double bond in compound 137. The hydrogen on nitrogen moved to C-3 and therefore, there was no N-H peak, but two hydrogens were connected with C-3 according to the $^1$H-NMR spectrum.

![Diagram](image)

Scheme 42

Wittig reaction of acetylated 2-trifluoroacetamido-2-deoxy-$\alpha$-D-glucopyranosyl aldehyde 132 with 1-triphenylphosphoranylidene-2-propanone: Synthesis of (E)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-$\alpha$-D-glucopyranosyl)-pent-3-en-2-one (139) and
4-acetonyl-(3,4,6-tri-O-acetyl-1,2-dideoxy-2-trifluoroacetamido-\(\alpha\)-D-glucopyrano)-[3,2-\(b\)]-pyrroldine (140). The acetylated 2-trifluoroacetamido-2-deoxy-\(\alpha\)-D-glucopyranosyl aldehyde 132 was treated with 1-triphenylphosphoranylidene-2-propanone in refluxing dry benzene for 18 h to give two products, \((E)\)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-\(\alpha\)-D-glucopyranosyl)-pent-3-en-2-one (139) in 67% yield and the 1,4-Michael addition bicyclo-product 140 in 31% yield. Compound 140 was identified according to the results of elemental analysis, MS, and NMR spectra. In the \(^1\)H- and \(^{13}\)C-NMR spectra of compound 140, there were no signals for N-H, for hydrogens connected with a double bond, non carbons of a double bond. Compound 140 was produced as a 1.40:1.00 mixture of \(4R\) and \(4S\) diastereoisomers. Compound 139 was obtained as a white sand-like crystals, having mp 124.5–125.5 °C and \([\alpha]_D +41.5^\circ\) in chloroform. The large coupling constant of \(J_{3,4} 16.0\) Hz indicated compound 139 to be the trans-isomer. The signal for N-H was at \(\delta 7.15\) as a doublet \((J_{NH,2^\prime} 9.2\) Hz), H-3 at \(\delta 6.17\) as a doublet \((J_{3,4} 16.0\) Hz), and H-4 at \(\delta 6.74\) as a doubled triplet \((J_{4,5a} = J_{4,5b} 7.0\) Hz and \(J_{3,4} 16.0\) Hz). In the \(^{13}\)C-NMR spectrum of 139, the peak at \(\delta 197.65\) was attributed to the conjugated ketone carbonyl group, and the peaks at \(\delta 141.31\) and \(\delta 133.52\) showed the presence of the double bond in compound 139.

The free-radical allylation reaction of 3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-\(\alpha\)-D-glucopyranosyl bromide (104) produced compound 105 as an \(\alpha,\beta\)-mixture in the ratio of 12:1. It was found difficult to separate this mixture with high yield. Thus, when the \(\alpha,\beta\)-mixture of compound 105 was ozononized, an \(\alpha,\beta\)-mixture of aldehyde 132 resulted. The Wittig reaction of the \(\alpha,\beta\)-mixture of aldehyde 132 with 1-triphenylphosphoranylidene-2-
propanone gave the product 139 as an $\alpha,\beta$-mixture, which could be efficiently separated on a column of silica gel, eluting with 1:1 CHCl$_3$-hexanes. The pure $\beta$-anomer of 139 was obtained as needle crystals having mp 188.5–189.5 °C and $[\alpha]_D$ -25.9° in chloroform, after recrystallization from 2:1 CHCl$_3$-hexanes.

\[
\begin{align*}
&\text{OBn} & \text{OBn} & \text{OBn} & \text{OBn} \\
&\text{BnO} & \text{BnO} & \text{BnO} & \text{BnO} \\
&\text{BnO} & \text{BnO} & \text{BnO} & \text{BnO} \\
\end{align*}
\]

i) CH$_3$NO$_2$/CH$_3$ONa/MeOH. ii) Ac$_2$O, NaOAc.

\text{Scheme 43}

**Synthesis of (E)-3-(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-1-nitro-1-propene (142).** The condensation of aldehydes with nitro compounds to give $\beta$-nitro alcohols (Henry reaction) is one of the most classic C-C bond-forming processes. The $\beta$-hydroxy group is acetylated or mesylated and then an elimination reaction gives the nitroalkene, either spontaneously or under the influence of mild base. The benzylated $\alpha$-D-glucopyranosyl $\alpha,\beta$-unsaturated nitroalkene 142 was synthesized in total 66% yield in two steps — nitroaldol condensation reaction of the benzylated $\alpha$-D-glucopyranosyl aldehyde 130 with nitromethane in methanolic sodium methoxide solution, and then acetylation and elimination reactions under the influence of the mild base sodium acetate.$^{113}$ The intermediate 141 from the
nitroaldol condensation reaction did not dissolve in methanol and precipitated out of the solution as the reaction continued. The nitroaldol condensation is reversible. To avoid it back to the starting materials, the intermediate 141 was used directly for acetylation and elimination reactions without purification and separation. The acetylation and elimination reactions were conducted in a suspension of sodium acetate in acetic anhydride at room temperature for 72 h. A white crystalline solid having mp 108.0–110.5 °C and [α]D +61.4° in chloroform was obtained after recrystallization of the crude product from methanol and 2-propanol. In the 1H-NMR spectrum of compound 142, the signal for H-1 was observed at δ 7.06 as a doublet (J1,2 13.5 Hz), that for H-2 at δ 7.26 as a doubled triplet (J2,3a = J2,3b 7.2 Hz and J1,2 13.5 Hz), and the signals for H-3a and H-3b were at 2.65 as multiplets. In the 13C-NMR spectrum, the peaks at δ 140.82 and 138.74 showed the presence of double bond from C-1 and C-2, and the signal for C-3 was at δ 24.98.

Scheme 44

Synthesis of (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-(triisopropylallyloxy)-penta-1,3-diene (143).
Compound 143 was synthesized in almost quantitative yield by the treatment of (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-pent-3-en-2-one (136) with the silylation reagent trisopropylsilyl trifluoromethanesulfonate under the influence of the bases potassium bis(trimethylsilyl)amide and triethylamine at -22 °C. The structure of 143 was identified from NMR and MS data. Compound 143 was not stable enough for elemental analysis and specific optical rotation, and it was used directly after work-up and rough purification on a short column of silica gel. In the 1H-NMR spectrum of compound 143, the signals for H-1a and H-1b appeared at δ 4.35 and δ 4.25 as singlets, respectively. The signal for H-3 was at δ 6.00 as a doublet (J3,4 15.2 Hz), and that for H-4 at δ 6.38 as a doubled triplet (J4,5a = J4,5b 7.3 Hz, and J3,4 15.2 Hz). The peaks for H-5a and H-5b were at δ 2.55 as multiplets, and those of isopropyl hydrogens from the silyloxy group were between δ 1.37–0.88. All of the data from 1H-NMR, 13C-NMR, and MS were consistent with the assigned structure of compound 143. From the results of the NOE enhancement of signals for H-1' (4.19%), H-5a (2.01%) and isopropyl hydrogens (1.86%) when H-4 was irradiated at δ 6.38, it was believed that compound 143 existed in the s-trans conformation in benzene-d6.

Figure 27. The NOE enhancement of compound 143
Figure 28. $^1$H-NMR spectrum of methyl (E)-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloth)-but-2-enoate (133)
Figure 29. $^{13}$C-NMR spectrum of methyl (E)-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-but-2-enoate (133)
Figure 30. $^1$H-NMR spectrum of methyl (E)-4-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxyl-α-D-glucopyranosyl)-but-2-enoate (134)
Figure 31. $^{13}$C-NMR spectrum of methyl (E)-4-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-$\alpha$-D-glucopyranosyl)-but-2-enoate (134)
Figure 32. $^1$H-NMR spectrum of methyl (E)-4-(3,4,6-tri-O-acetyl-2-deoxy-2-
trifluoroacetamido-α-D-glucopyranosyl)-but-2-enoate (135)
Figure 33. $^{13}$C-NMR spectrum of methyl (E)-4-(3,4,6-tri-O-acetyl-2-deoxy-2-
trifluoroacetamido-$\alpha$-D-glucopyranosyl)-but-2-enoate (135)
Figure 34. $^1$H-NMR spectrum of methyl (E)-4-(3,4,6-tri-O-acetyl-2-deoxy-2-
trifluoroacetamido-$\beta$-D-glucopyranosyl)-but-2-enoate (135$\beta$)
Figure 35. $^{1}$H-NMR spectrum of \((E)-5-(2,3,4,6\text{-tetra-}O\text{-benzyl}\text{-}\alpha \text{-}D\text{-glucopyranosyl})\text{-pent-3-en-2-one (136)}$
Figure 36. $^{13}$C-NMR spectrum of (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-pent-3-en-2-one (136)
Figure 37. $^1$H-NMR spectrum of 4(8)-acetonyl-(2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-\(\alpha\)-D-glucopyrano)-[3,2-\(\beta\)]-pyrrolidine (138)
Figure 38. $^{13}$C-NMR spectrum of 4(R)-acetonyl-(2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyrano)-[3,2-b]pyrrolidine (138)
Figure 39. $^1$H-NMR spectrum of (E)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-
trifluoroacetamido-α-D-glucopyranosyl)-pent-3-en-2-one (139)
Figure 40. $^{13}$C-NMR spectrum of (E)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)-pent-3-en-2-one (139)
Figure 41. $^1$H-NMR spectrum of (E)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-
trifluoroacetamido-β-D-glucopyranosyl)-pent-3-en-2-one (139β)
Figure 42. $^{13}$C-NMR spectrum of (E)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-
strifluoroacetamido-$\beta$-D-glucopyranosyl)-pent-3-en-2-one (139$\beta$)
Figure 43. $^1$H-NMR spectrum of 4-acetonyl-(3,4,6-tri-O-acetyl-1,2-dideoxy-2-trifluoroacetamido-α-D-glucopyran)-[3,2-b]-pyrrolidine (140)
Figure 44. $^{13}$C-NMR spectrum of 4-acetonyl-(3,4,6-tri-O-acetyl-1,2-dideoxy-2-
trifluoroacetamido-α-D-glucopyran)-[3,2-b]-pyrrolidine (140)
Figure 45. $^1$H-NMR spectrum of (E)-3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-nitro-1-propene (142)
Figure 46. $^{13}$C-NMR spectrum of (E)-3-(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-1-nitro-1-propene (142)
Figure 47. $^1$H-NMR spectrum of (E)-5-(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-2-(triisopropylsilyloxy)-penta-1,3-diene (143)
Figure 48. $^{13}$C-NMR spectrum of (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-(triisopropylsilyloxy)-penta-1,3-diene (143)
C. Diels–Alder Cyclization Reactions of C-Linked Glycosylalkenes and C-Linked Glycosylalkadienes

The Diels–Alder reaction is one of a general class of cycloaddition reactions that leads to the formation of a wide range of six-membered carbocyclic and heterocyclic structures. Both inter- and intra-molecular reactions have been employed in the synthesis of numerous natural products. In many cases the Diels–Alder reaction takes place readily at ambient or slightly elevated temperatures. Reactions that are sluggish or which involve thermally unstable reactants or lead to unstable products can often be accelerated by catalysts or by conducting the reaction at high pressures. Most Diels–Alder reactions involve a diene carrying electron-donating substituents (e.g. alkyl, alkoxy) and a dienophile bearing electron-attracting substituents (for example, CO, CN, NO₂). The value of the Diels–Alder reaction in synthesis is due in large measure to its high regio- and stereo-selectivity. The reaction of an unsymmetrical diene with an unsymmetrical dienophile could, in principle, give rise to two regioisomeric adducts, but in practice one product generally predominates. The high stereoselectivity in the Diels–Alder reaction is probably the factor more than any other which has led to its widespread application in the synthesis of complex natural products. Up to four new chiral centers may be built up in the reaction between a diene and a dienophile, but it is frequently found that one of the several possible racemates is formed in preponderant amount or even exclusively. If either the diene or the dienophile is chiral and optically active, facially selective addition will give rise to a non-statistical mixture of optically active diastereomers. The more facially-selective the addition the more diastereoselective the reaction will be until, in the ideal
case, a single diastereomer results. Usually the chiral center is incorporated in
the diene or dienophile at an allylic position. Currently, the more active area of
research with asymmetric Diels–Alder reactions is to conduct the reactions
using non-optically active dienes and dienophiles in the presence of an
optically active catalyst, or to temporarily attaching to the diene or dienophile an
optically active auxiliary group that is later removed from the diastereomerically
pure adduct to give an enantiomerically pure product.115

Diels–Alder reactions of carbohydrate derivatives comprise an important
method for the synthesis of carbocyclic compounds in optically active form. In
recent studies, Diels–Alder adducts obtained from carbohydrate substrates
have been used as intermediates in the approaches to complex natural
products, as summarized previously. The carbohydrate substrates have also
been used as the chiral auxiliary to construct chiral dienes and dienophiles, or
chiral catalysts, to improve the regio- and stereo-selectivity of Diels–Alder
reactions. However, the behavior of the Diels–Alder reaction of C-
glycosylalkenes and C-glycosylalkadienes has not been investigated thus far,
although this is extremely attractive for the synthesis of
"pseudooligosaccharides", and other carbocyclic natural compounds having C-
glycosyl subunits. Here, a series of C-glycosylalkenes and C-glycosylalkadienes
has been synthesized, and their reactivity, regio- and stereo-selectivity in the
Diels–Alder reaction is studied in detail.

1. Diels–Alder reactions of C-linked glycosylalkenes with (E)-1-methoxy-3-
   (trimethylsilyloxy)-1,3-butadiene
(E)-1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene is very reactive diene, since the activating effects of the two electron-donating substituents reinforce each other. It can be obtained commercially, or by enol silylation of the methoxyenone,\(^{116}\) and has been employed in the synthesis of a variety of natural products to form cyclic enol ethers, which give cyclohexanones on hydrolysis. The cycloaddition reactions of (E)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene with C-glycopyranosylalkenes 142, 134, 133, 135, 136 and 139 were investigated first.
Diels–Alder reaction of α,β-unsaturated nitroalkene 142 with (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene. (E)-3-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)-1-nitro-1-propene (142) was treated with an excess of (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene in refluxing toluene for 16 h. The solution was then hydrolyzed with an 0.5 M HCl solution in THF to
give four cyclohexanone products 144, 145, 146, and 147 in 83% total yield. The mixture of four products gave a spot with long trail in TLC (Rf 0.38, 1:1 hexanes–ether), and the exo-adducts 144 and 145 (202.8 mg, 66.5%) were eluted out first during purification on a column of silica gel, and the endo-adducts 146 and 147 (49.9 mg, 16.4%) was obtained later. The ratio of exo:endo additions was 80:20. The ratio of facial selectivity for both exo-addition and endo-addition was determined by integrations of the single methoxy peaks from 1H-NMR spectra. The two methoxy signals in the 1H-NMR spectrum of the exo-adducts were appeared at δ 3.33 and 3.31 in a ratio of 53:47, and those of endo-adducts were at δ 3.29 and 3.28 in a ratio of 45:55. Thus the facial selectivity for exo-addition was 53:47 and that for endo-addition 55:45.

A single white crystalline diastereomer of the exo-adduct was obtained after recrystallization of the mixture of exo-adducts from 5:1 hexanes–EtOAc. It had mp 134–135 °C and [α]D +22.8° in chloroform, and is arbitrarily named 144a. The relative configuration of the single exo-diastereomer 144a was determined by 1H- and 13C-NMR spectra. The cyclohexanone ring is numbered in the way to make the carbonyl group in position 1, methoxy group in position 3, and the sugar methyl group in position 5. In the 1H-NMR spectrum of 144a, H-4 resonated at δ 4.66 as a triplet (J4,5 = 10.5 Hz), which indicated that the sugar methyl group at C-5, nitro substituent at C-4 and methoxy group at C-3 were all in equatorial disposition and compound 144a was the exo-addition product. The signals for H-3 and H-1' were overlapped at δ 3.93 as multiples. The methoxy peak was at δ 3.33 as a singlet. H-2e and H-2a were resonated at δ 2.92 as a doubled doublet of a doublet (J2a,2a = 14.5 Hz, J2e,3 5.0 Hz and J2a,6e 1.7 Hz), and δ 2.38 as a doubled doublet (J2a,3 10.7 Hz
and $J_{2e,2a} = 14.5$ Hz), respectively, which also demonstrated that the methoxy group at C-3 was in an equatorial position. H-6e and H-6a resonated at $\delta = 2.76$ as a doubled doublet of a doublet ($J_{6e,6a} = 14.8$ Hz, $J_{5,6a} = 4.5$ Hz and $J_{2a,6e} = 1.7$ Hz), and $\delta = 2.19$ as a doubled doublet ($J_{5,6a} = 13.6$ Hz and $J_{6e,6a} = 14.8$ Hz), respectively. The signal for H-5 was at $\delta = 2.44$ as a multiplet, and those for H-7R and H-7S were at $\delta = 1.90$ and $\delta = 1.75$, respectively. In the $^{13}$C-NMR spectrum, the peak at $\delta = 203.65$ clearly indicated the presence of the ketone carbonyl group. The absolute configuration of compound 144a could not be determined by the single crystal X-ray diffraction analysis because of the difficulty in obtaining a suitable large single crystal.

Assignment of the absolute configuration of compound 144a was attempted by the coupling constants, $^1$H-$^1$H NOESY and ROESY spectra of related compounds, and the results on the favored conformations of C-glycosyl compounds.

Kishi has extensively investigated the favored conformations of C-glycosyl compounds.\textsuperscript{117} The conformational analysis of small oligosaccharides has received much attention because of the importance of three-dimensional structure of oligosaccharides in biological functions. The anomeric and exo-anomeric effects play an important role in determining the favored conformations of sugars. Regarding the O-R bond at the anomeric center, there are three staggered rotamers 148A, 148B, and 148C around the glycosidic bond of an $\alpha$-glycoside. The $\alpha$-glycoside 148 is known to favor conformer 148A over the conformer 148B and 148C because of (1) steric destabilization of 148C over 148A and 148C, (2) stereoelectronic stabilization of 148A (and 148C) over 148B (exo-anomeric effect), and (3) steric destabilization of 148B over 148A. This holds true for both oligosaccharides and simple O-alkyl
glycosides. The difference between the conformational behavior of parent glycosides and corresponding C-glycosyl compounds is that the anomeric and exo-anomeric effects play no role in C-glycosyl compounds. There are no rigorous experimental data available to estimate the degree of the stabilization from the exo-anomeric effect. The vicinal coupling constants between the C-1 and C-α protons were used to study the conformations of the carbon analogues of glycosides around the C-glycosyl linkage by Kishi.\textsuperscript{117} The axial carbon monoglycosides 150, 151 and 152 were synthesized from the corresponding
allyl "C-glycosides". According to the Karplus equation, two antiperiplanar vicinal protons will have a coupling constant of ca. 13 Hz, whereas two gauche protons will have a coupling of ca. 3 Hz. The observed coupling constants around the C-glycosylic bond for the α-C-glycosyl derivatives 150 (11.4, 3.1 Hz), 151 (11.3, 3.3 Hz), and 152 (10.1, 4.1 Hz) indicate a marked preference for either conformer 149A or conformer 149B. In order to differentiate unambiguously between the two possible conformers, the stereospecifically α-labeled analogues 150cfa, 151c/r, and 152c/s were synthesized. The absolute stereochemistry of the C-α proton responsible for each methylene signal and corresponding coupling constants in the 1H-NMR spectrum were assigned by comparison of the 1H-NMR spectra of 150, 151 and 152 with those of 150dR, 151dR, and 152dS. The assignment of the absolute stereochemistry of the proton with the large coupling constant as pro-S in all three cases indicated that the α-C-glycosyl derivatives 150, 151 and 152 have a strong preference for the conformation around the C-glycosylic C-1–C-α bond with the C-α–C-β bond antiperiplanar to the C-2–C-1 bond (conformer 149A). The magnitude of the coupling constants excludes a substantial contribution from other conformers. The 2-deoxy analogues of 150, 151, and 152 were also synthesized and a comparison of the coupling constants around the C-glycosylic bond shows little effect upon removal of the oxygen at the 2-position.
of the pyranose ring. This experimental observation rules out a 1,3-diaxial-like interaction between the C-2–O-2 and C-α–C-β bonds as the primary factor in controlling the conformational behavior of these compounds. The conformational preference of C-glycosyl compounds around the C-glycosylic bond in favor of conformer 149A must be attributed predominantly to gauche interactions. It is therefore independent of the structure and stereochemistry of the substituents of the pyranose ring. The same methodology was used to study the preferred conformation of carbon analogues of 1→6-disaccharides and 1→4-disaccharides. The experimental results showed that the α-(1→6)-C-diglucose 153 favored the conformer 153A, and the α-(1→4)-C-disaccharide 154 favored the conformer 154A. The C-disaccharides are, like
the corresponding parent disaccharides, not conformationally rigid. Nonetheless, the weighted average of available conformers corresponds extremely well to the one predicted (C-α–C-β bond antiperiplanar to C-1–C-2 bond). The conformation of 1→6-linked disaccharides may be analyzed in terms of independent monoglucosylic systems. In the 1→4-linked disaccharides, the conformational preference around the C-glycosylic bond is so overwhelming that a structure deviation from the ideal staggered conformer to avoid the steric interactions takes place by rotating primarily the nonglycosylic C-4–C-α bond rather than the glycosylic C-1′–C-α bond. The recognition of this phenomenon allows prediction the conformation behavior of di-C-saccharides and higher C-saccharides, and their parent substances. The conformation of the carbon analogue 155 of 3-O-α-D-galactopyranosyl-D-galactopyranose was predicted to be restricted to one unique conformer 155A, and NMR data confirmed this prediction.

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\text{155}
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\text{155A}
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According to Kishi's results concerning the conformational preference of C-glycosyl compounds around the C-glycosylic bond with the C-1–C-2 bond in the tetrahydropyran ring antiperiplanar to the C-α–C-β bond, it may be
predicted that compound 144 could exist in three possible conformers 144A, 144B, and 144C, and compound 145 in the possible conformers 145A, 145B, and 145. Among the three ideal staggered conformers 144A, 144B, and 144C available for compound 144, conformer 144C is considered to be the least favored because of the steric interactions around the C-7–C-1' bond surrounded by the C-5–C-4 and C-5–C-6 bonds. 1,3-Diaxial-like interactions are evident in both conformers 144A (between the C-1'O-5 bond and the C-5–C-6 bond), and 144B (between the C-7–C-1' bond and the C-4–NO₂ bond). However, the 1,3-diaxial-like interaction between the C-7–C-1' bond and the C-4–NO₂ bond is much stronger than that between the C-1'O-5 bond and the C-5–C-6 bond since the C-4–NO₂ bond is much more polar than the C-1'O-5 bond, and the NO₂ substituent is larger than the single oxygen atom. As a result, conformer 144A is anticipated to be the most favored conformer. For the same reasons, conformer 145C for compound 145 seems to suffer from the most severe steric interactions among the three possible conformers 145A, 145B, and 145C, since the C-7–C-1' bond is surrounded by the C-5–C-4 and C-5–C-6 bonds. There are two 1,3-diaxial-like interactions in conformer 145B (C-7–C-1'C-4–NO₂ and C-1'O-5/C-5–C-4) and none in conformer 145A. Thus, conformer 145A is the most stable conformer among conformers 145A, 145B, and 145C. The spin–spin coupling constants for the C-7 protons in conformer 144A are predicted to be $J_{1'7S} \sim 10$ Hz, $J_{1'7R} \sim 3$ Hz, $J_{7S,5} \sim 10$ Hz, $J_{7R,5} \sim 3$ Hz, and $J_{7R,7S} \sim 15$ Hz, and there should be cross peaks between H-1' and H-5, and H-7S and H-5' in the $^1$H-$^1$H NOESY spectrum of conformer 144A. The spin–spin coupling constants for the C-7 protons in conformer 145A are predicted to be $J_{1'7S} \sim 10$ Hz, $J_{1'7R} \sim 3$ Hz, $J_{7S,5} \sim 3$ Hz, $J_{7R,5} \sim 10$ Hz, and $J_{7R,7S} \sim 15$ Hz, and there should be no cross peaks between H-1' and H-5.
in the $^1$H-$^1$H NOESY spectrum of conformer 145A.

In the $^1$H-NMR spectrum of the exo-adduct 144a, H-7S resonated at $\delta$ 1.75 (ddd, $J_{1',7S}$ 10.8 Hz, $J_{5,7S}$ 7.3 Hz and $J_{7R,7S}$ 15.3 Hz), and H-7R resonated at $\delta$ 1.90 (ddd, $J_{1',7R}$ 2.6 Hz, $J_{5,7R}$ 3.8 Hz, $J_{7R,7S}$ 15.3 Hz). H-7S and H-7R were assigned according to Kishi's conclusion that the pro-$S$ hydrogen at Cα (adjacent to the anomeric carbon in the sugar ring) has large coupling constant with H-1' in the sugar ring and the C-α-C-β bond is antiperiplanar to the C-2'-C-1' bond. In the $^1$H-$^1$H NOESY spectrum of compound 144a, there were cross-peaks between H-1' and H-5, and H-7S and H-5' or H-3'. By comparison of the NMR data obtained from compound 144a with those predicted for conformers 144A and 145A, it is concluded that compound 144a should have the absolute configuration of (3S, 4S, 5R)-5-[(2,3,4,6-tetra-$O$-benzyl-$\alpha$-$D$-glucopyranosyl)methyl]-3-methoxy-4-nitrocyclohexanone (144). The coupling constants of $J_{7S}$ 7.3 Hz and $J_{7R}$ 3.8 Hz suggested that compound 144 exists predominantly in the staggered conformer 144A, or in a conformer slightly deviated from conformer 144A. This conclusion is further supported by the NMR data of compound 155, which was synthesized and will be described later. Structurally, the methoxy group in compounds 144, or 145 is replaced by a (2,3,4,6-tetra-$O$-benzyl-$\alpha$-$D$-glucopyranosyl)methyl group to give compound 155. The central cyclohexanone ring in compound 155 is numbered clockwise with the carbonyl group in position 1 (the same way as in compound 144). The conformational behavior of compound 155 around C-5 should be the same as that in compound 144, which favors conformer 144A with the C-7–C-1' bond antiperiplanar to the C-5–C-4 bond. The conformation of compound 155 around C-3 should be similar to that of compound 145, which shows conformer 145A to be the most favored. By a combination of the most favored conformers
In compounds 144 and 145, it is predicted that conformer 155A is the most stable conformer for compound 155. The NMR data of compound 155 confirmed the prediction. In the $^1$H-NMR spectrum of compound 155, H-7S resonated at $\delta$ 1.46 (ddd, $J_{1',7S}$ 9.3 Hz, $J_{5,7S}$ 9.7 Hz and $J_{7R,7S}$ 15.0 Hz), H-7R
at $\delta$ 1.83 (ddd, $J_{1',7R}$ -2 Hz, $J_{5,7R}$ -2 Hz and $J_{7R,7S}$ 15.0 Hz), H-7'S at $\delta$ 1.97 (ddd, $J_{1'',7S}$ 12.2 Hz, $J_{3,7S}$ -2 Hz and $J_{7R,7S}$ 14.7 Hz), and H-7'R at $\delta$ 1.55 (ddd, $J_{1'',7R}$ 2.5 Hz, $J_{3,7R}$ 10.2 Hz and $J_{7R,7S}$ 14.7 Hz). The coupling constants observed for hydrogens at C-7 and C-7' suggested that the C-1'-C-2' bond is antiperiplanar to the C-7-C-5 bond, the C-7-C-1' bond antiperiplanar to the C-5-C-4 bond, and the C-1''-C-2'' bond antiperiplanar to the C-7'-C-3 bond, the C-7'-C-1'' bond antiperiplanar to the C-3-C-4 bond, which is consistent with conformer 155A. The two dimension proton ROESY spectrum of compound 155 in benzene-$d_6$ further confirmed compound 155 exists in the conformer 155A. The results of hydrogen correlations in the $^1$H-$^1$H ROESY spectrum of compound 155 are summarized in Table 9. Some of the important hydrogen correlations in determining the conformational behavior around C-3 and C-5 in compound 155 are shown in Figure 28. NOE intensities in the ROESY spectrum of compound 155 are arbitrarily assigned as "strong" (s), "medium" (m), and "weak" (w) and correspond to the different ranges of distances between two hydrogens. The relative intensities of ROESY cross-peaks were evaluated from the 2D contours, based on visual comparisons of the intensities of the geminal and vicinal ROESY cross-peaks relative to cross-peaks corresponding to long-range dipolar interactions. In the ROESY spectrum of compound 155, the strong cross peaks are observed between the geminally related H-2e and H-2a, H-6e and H-6a, H-7S and H-7R, H-7'S and H-7'R, whereas medium-intensity cross-peaks are observed between the 1,3-diaxially related H-2a/H-6a/ H-4, and H-3/H-5. Medium-intensity cross-peaks are also present between H-7S and H-5' or H-3', H-7'S and H-5'' or H-3''. A cross-peak between H-7S and H-4 is observed, with an intensity between medium and weak-intensity. A medium-intensity cross-peak between H-1' and
Table 9. $^1$H-$^1$H correlations in the two-dimension ROESY spectrum of compound 155.

<table>
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<tr>
<th></th>
<th>H-2e</th>
<th>H-2a</th>
<th>H-3</th>
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Figure 49. Some important correlations in the $^1$H-$^1$H ROESY spectrum of 155.
H-5, and relatively weak-intensity cross-peaks between H-1' and H-7R, as well as H-5 and H-7R, indicate that the conformation around C-5 in compound 155 is the same as conformer 144A with the C-1'-C-2' bond antiperiplanar to the C-7-C-5 bond, and the C-7-C-1' bond antiperiplanar to the C-5-C-4 bond. There is no cross-peak between H-3 and H-1", but medium-intensity cross-peaks are observed between H-1" and H-2a, H-1" and H-7'R, H-7'R and H-4. These results indicate that the conformation around C-3 in compound 155 is the same as the predicted conformer 145A with the C-1"-C-2" bond antiperiplanar to the C-7'-C-3 bond, and the C-7'-C-1" bond antiperiplanar to the C-3-C-4 bond. The fact that compound 155 exists in conformer 155A, and the 1H-NMR spectrum and 1H-1H NOESY spectrum of the exo-adduct 144a are consistent with the predicted conformer 144A demonstrates compound 144a to be the exo-diastereomer 144, and not 145. This conclusion is based on the assumption that Kishi's results concerning the favored conformations of C-glycosyl compound (the C-1-C-2 bond antiperiplanar to the C-α-C-β bond) can be applied to the pseudo-C-disaccharide.
Diels–Alder reaction of α,β-unsaturated ester 134 with (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene. The cycloaddition reaction of methyl (E)-4-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-but-2-enoate (134) with (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene in dry xylene at 225 °C for 24 h afforded four diastereomeric products 156, 157, 158,
and 159 in 73% total yield, after hydrolysis of the cycloaddition solution with 1 M Bu₄NF in THF and purification on a column of silica gel eluting with EtOAc. The ratio of the products was determined by integrations of the single methoxy peaks and N-H peaks in the ¹H-NMR spectra of the products. The two methoxy peaks for the exo-adducts (156 and 157) were at δ 3.32 and δ 3.30. Both endo-adducts 158 and 159 showed the methoxy peaks at δ 3.36, but different chemical shifts for N-H, which were resonated at δ 6.46 and δ 5.89, respectively. It was determined that the ratio of exo-addition to endo-addition was 73:27. The facial selectivity for exo-addition was 56:44, and that for endo-addition 54:46.

TLC of the products showed a long trailing spot, with the exo-adducts at the top followed by the endo-adducts. Evaporation of the first several fractions from chromatographic purification gave a white solid that was recrystallized from 2:1 hexanes–CHCl₃ to afford a colorless long needle crystal having mp 183–184 °C and [α]D +29° in chloroform. NMR data showed that it was a single exo-addition diastereomer. The relative configuration of this exo-diastereomer was determined by its NMR spectra. The central cyclohexanone ring is numbered in the way to make carbonyl carbon at position 1, the methoxy group at position 3 and the sugar methyl group at position 5. In the ¹H-NMR spectrum, N-H proton resonated at δ 5.99 as a doublet (JₙH₂, 2 8.8 Hz), and there was a single methoxy peak at δ 3.30. The signals for H-4 and H-6e overlapped together at δ 2.67. The H-3 atom resonated at δ 3.73 as a doubled doublet of a doublet (J₃, 2 3.4 Hz, J₃, 2 9.5 Hz, and J₃, 4 8.2 Hz), indicating that the methoxy group at C-3 was in an equatorial disposition, and the crystalline product was an exo-addition product. From the ¹³C-NMR spectrum, the signal at δ 206.32 showed the presence of the ketone carbonyl group. The results of elemental analysis indicated that the crystalline sample co-existed with the solvent
chloroform with a ratio of 1.00:0.25. The absolute configuration cannot be
determined by the single crystal X-ray diffraction analysis because of the
difficulty in obtaining a large single crystal.

When the cycloaddition solution was hydrolyzed with 3% HCl, instead of
Bu₄NF, an α,β-elimination reaction occurred in the endo-adducts to give the
α,β-unsaturated cyclohexenone products. TLC of the mixture showed a long
trailing spot with the cyclohexenone products at the top. Evaporation of the last
few fractions from the chromatographic purification gave a white solid, which
was recrystallized from 1:1 hexanes–EtOAc to provide colorless needles having
mp 194–195 °C and [α]D +54.3° in chloroform. NMR data demonstrated that it
was another exo-addition diastereomer. The relative configuration of the
second exo-addition diastereomer was determined by NMR spectroscopy. The
central cyclohexanone ring is numbered in the way to make carbonyl carbon at
position 1, the methoxy group at position 3 and the sugar methyl group at
position 5. In the ¹H-NMR spectrum, N-H resonated at δ 5.86 as a doublet
(\(J_{NH,2}\) 7.9 Hz), and the single methoxy peak at δ 3.32. The signals for H-4 at δ
2.63 as a doubled doublet (\(J_{3,4}\) 9.1 Hz and \(J_{4,5}\) 10.5 Hz) and H-3 at δ 3.68 as a
doubled doublet of a doublet (\(J_{2a,3}\) 4.4 Hz, \(J_{2a,3}\) 10.4 Hz, and \(J_{3,4}\) 9.1 Hz)
indicated that all of the three substituents at C-3, C-4, and C-5 were at
equatorial positions and the product was the exo-addition product. In the ¹³C-
NMR spectrum, the signal at δ 205.59 demonstrated the presence of the ketone
carbonyl group. The absolute configuration again could not be determined by
the single crystal X-ray diffraction analysis because of the difficulty in obtaining
a large single crystal.
Diels–Alder reactions of \( \alpha\)-C-glycopyranosyl alkenes 133, 135, 136 and 139 with \((E)\)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene. The cycloaddition reactions of sugar dienophiles 133, 135, 136 and 139 with \((E)\)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene were run in a conical reaction vial in dry xylene for 24 h at 190–215 °C. The cycloaddition intermediates were hydrolyzed with 1 M Bu4NF in THF and the crude products were purified on a column of silica gel. There were four diastereomeric products from each cycloaddition reaction. The ratio of the products was determined by integrations of the single methoxy peaks in \(^1\)H-NMR spectra. None of the foregoing four cycloaddition reactions afforded a single crystalline product.

The yields and stereoselectivities of the Diels–Alder reactions of \( \alpha\)-C-glycopyranosyl alkenes 142, 134, 133, 135, 136, and 139 with \((E)\)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene are summarized in Table 10. The cycloaddition reactions provide four diastereomeric products with reasonably good net yields. Under the thermal cycloaddition conditions, all of the \( \alpha\)-C-glycopyranosylalkenes investigated favored the exo-addition, thus not obeying the endo rule. The Alder endo rule states that the diene and dienophile arrange themselves in parallel planes and the most stable transition-state is that in which there is maximum accumulation of double bonds, or the maximum possibility of orbital overlap. The pathway in the Diels–Alder cycloaddition reaction of \( \alpha\)-C-glycosylalkenes is shown in Figure 29. The preference of exo-addition may be explained by the coordinating stabilization between the silicon atom and oxygen or nitrogen atoms in the tetrahydropyran ring and the C-2' position in the transition state. In the endo-addition, the trimethylsilyloxy group
Table 10. Stereoselectivity in cycloaddition reactions of α-C-glycosylalkenes with \((E)-1\text{-methoxy}-3\text{-}(\text{trimethylsilyloxy})\text{-1,3-butadiene}\)

<table>
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<tr>
<th>Dienophile</th>
<th>Yield (%)</th>
<th>\textit{Exo}:Endo in the \textit{Exo}-Addition</th>
<th>Facial-Selectivity in the \textit{Exo}-Addition</th>
<th>Facial-Selectivity in the \textit{Endo}-Addition</th>
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<td>73:27</td>
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<td>82</td>
<td>75:25</td>
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<td>80</td>
<td>77:23</td>
<td>59:41</td>
<td>66:34</td>
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</tbody>
</table>
Figure 50. Diels–Alder reactions of α-C-glycosylalkenes with (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene
is remote from the sugar ring, and it is impossible to form a long-distant complex between the silicon atom and heteroatoms of the sugar. In the exo-addition, the trimethylsilyloxy group can form a weak complex with the ring oxygen when attacking from the down-face, and form a weak complex with the oxygen or nitrogen at C-2' when attacking from the up-face in the transition state, and this may help to stabilize the transition state. The cycloaddition reaction of α-C-glycosylalkenes with (E)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene showed good yields and high exo-endo selectivities, but relative low diastereofacial selectivities in both exo- and endo-addition. The diastereofacial selectivity in the cycloaddition reaction is largely controlled by the stereochemistry of the allylic atom. In the α-C-glycosylalkenes, the methylene group is located at the allylic position, which will not influence the facial selectivity of the dienophile. The diastereofacial selectivity for the α-C-glycosylalkene should be controlled by remote effects from the sugar moiety. In both exo- and endo-additions, attack from the up-face is hindered by the substituent at C-2' in the sugar ring, and addition from the down-face is hindered by the lone-pair electrons of the ring oxygen and the substituent at C-6'. The low diastereofacial selectivity suggests that the impediments from both side are similar, or that the sugar chiral centers sterically are too remote to control on the facial selectivity.

2. **Diels–Alder reactions of C-linked glycosylalkenes with the C-linked glycosyl alkadiene**

The C-glycosylalkadiene (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-(trimethylsilyloxy)-penta-1,3-diene (143) was synthesized
from (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-pent-3-en-2-one (136) in quantitative yield. It was evaluated as a possible α-C-glycosyl diene for the cycloaddition reaction for producing *pseudo*-trisaccharide with a sugar dienophile in a single step. The Diels–Alder reaction of α-C-glycosyl alkenes 133, 136, 142, and 134 with α-C-glycosyl diene 143 was investigated in detail.

Scheme 47

**Diels–Alder reaction of methyl (E)-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-but-2-enoate (133) with α-C-glycosyl diene 143.** The α-C-glycosyl diene 143 was treated with α-C-glycosyl dienophile
133 in dry xylene at 250 °C for 96 h, and then the solution was hydrolyzed with 1 M Bu₄NF in THF. After purification on a column of silica gel and recrystallization from 4:1 hexanes–EtOAc, a white crystalline product having mp 101–102 °C and [α]D +36.7° in chloroform was obtained in 34% yield. The product was characterized by elemental analysis, MS, optical specific rotation, and NMR spectra. It was demonstrated that the product was a single exo-addition product 160. No endo-adducts could be detected by NMR in mother liquors. Theoretically, there are eight possible cycloaddition products, but the silyloxy group in the diene exerts a very strong regio-selectivity and the cycloaddition reaction gives four possible adducts—two endo-adducts and two exo-adducts with the silyloxy group from the diene and the electron-withdrawing group in the dienophile in the para-relationship in the adducts. As the two sugar components in the sugar dienophile 133 and the sugar diene 143 are the same, only one exo-adduct will be produced. In the ¹H-NMR spectrum of product 160, H-4 resonated at δ 2.21 as a triplet (J₃,₄ = J₄,₅ 10.9 Hz), indicating the three substituents at C-3, C-4, and C-5 were all in equatorial positions and the product was the exo-addition product. In the ¹³C-NMR spectrum, the peak at δ 208.17 demonstrated the presence of the ketone carbonyl group in compound 160.

**Diels–Alder reaction of (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-penten-3-en-2-one (136) with α-C-glycosyl diene 143.** The Diels–Alder reaction of sugar dienophile 136 and sugar diene 143 was carried out in a reaction vial in dry xylene for 96 h at 240–245 °C. The mixture was hydrolyzed in 3% HCl in acetone, purified on a column of silica gel and recrystallized from 4:1 hexanes–ether to afford a white crystalline product.
having mp 140.5–141.5 °C and [α]D +34.7° in 48% yield. It was demonstrated by NMR spectra that this compound was the exo-addition product 161. The endo-adducts could not be detected by NMR in the original chromatographic fractions. In the 1H-NMR spectrum of product 161, the signal for H-5 was at δ 2.35 as a triplet (J3,4 = J4,5 10.2 Hz), which established the equatorial relationship among the three substituents at C-3, C-4 and C-5 in the central cyclohexanone ring and that the compound was the exo-addition product. In the 13C-NMR spectrum, the signals at δ 211.30 and δ 208.49 indicated that there were two ketone carbonyl groups in the product, one belonging to the methyl ketone substituent at C-4 and one belonging to the carbonyl group in the central cyclohexanone ring.

The Diels–Alder reaction of sugar dienophile 136 and sugar diene 143 under the Lewis acid catalysis was also investigated. The cycloaddition reaction catalyzed by BF3·OEt2 provided the adduct 161 in only 5% yield. The same reaction under SnCl4 catalysis afforded a mixture of unseparable products. There were no cycloaddition products detected under the catalysis by TiCl4, which led to the 1,4-addition product 5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-4-chloro-2-pentanone as the major product.

Diels–Alder reaction of (E)-3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-nitro-1-propene (142) with α-C-glycosyl diene 143. The cycloaddition reaction of sugar dienophile 142 and sugar diene 143 was run in a reaction vial in dry xylene for 24 h at 210–215 °C. The cycloaddition intermediate was hydrolyzed in 3% HCl in acetone to remove the silyl group and produce the cyclohexanone ring. The crude products were purified on a column of silica gel and recrystallized from 3:1 hexanes–toluene to
give a white crystalline product having mp 148–149 °C and [α]D +34° in chloroform in 41% yield. The NMR spectra of the product showed that it was the single exo-addition product 155. The endo-adducts could not be detected by NMR methods from the samples of the original chromatography fractions. In the 1H-NMR spectrum of product 155, H-4 resonated at δ 4.11 as a triplet (J3,4 = J4,5 10.9 Hz), which indicated the substituents at C-3, C-4 and C-5 to be in equatorial positions and the product was an exo-addition product. In the 13C-NMR spectrum, the signal at δ 207.14 showed the presence of ketone carbonyl group.
Diels–Alder reaction of methyl (E)-4-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-but-2-enoate (134) with α-C-glycosyl diene 143. The cycloaddition reaction of α-C-glycosyl alkene 134 with α-C-glycosyl alkydiene 143 was run in a reaction vial in dry xylene at 230 °C for 72 h. The reaction solution was hydrolyzed in 1 M Bu₄NF in THF and purified on a column of silica gel. Two separable exo-adducts 162a and 162b were obtained in 22% total yield. The ratio of the two exo-adducts was 51:49, which was also the diastereofacial selectivity. The first white crystalline exo-adduct (R_f 0.68, EtOAc) had mp 144–145 °C and [α]_D +37.0° in chloroform, and
is arbitrarily named 162a. The second white crystalline exo-adduct (Rf 0.59, EtOAc) had mp 164–166 °C and [α]D +70.6° in chloroform, and is arbitrarily named 162b. The central cyclohexanone ring of the cycloaddition adducts 162a and 162b is numbered so as to make the (2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)methyl group located at C-3 and (2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)methyl group located at C-5. The absolute configuration of the exo-diastereomers 162a and 162b could not be determined by the single crystal X-ray diffraction analysis because of the difficulty in obtaining a large single crystal. The relative configuration was determined by the NMR spectra. In the 1H-NMR spectrum of exo-adduct 162a, there were four single acetyl peaks and eight benzyl hydrogen peaks, which indicated the presence of both sugar components from the sugar diene and sugar dieophile in the adduct. The signal for the methoxy carbonyl hydrogens was at δ 3.47 as a singlet. H-6e resonated at δ 2.71 as a doubled doublet (J_{6e,6a} 14.4 Hz and J_{6e,5} 2.7 Hz) and H-2e at δ 2.64 also as a doubled doublet (J_{2e,2a} 14.3 Hz and J_{2e,3} 3.0 Hz). The signal for H-4 was at δ 2.18 as a triplet (J_{3,4} = J_{4,5} 10.8 Hz), which indicated the three substituents at C-3, C-4 and C-5 all to be in equatorial positions and the adduct 162a to be an exo-addition product. In the 13C-NMR spectrum of adduct 162a, the signal at δ 207.34 indicated the presence of a ketone carbonyl group in the product. In the 1H-NMR spectrum of product 162b, the signal for the methoxy carbonyl hydrogens was at δ 3.39 as a singlet. H-6e resonated at δ 3.02 as a doubled doublet (J_{6e,6a} 14.4 Hz and J_{6e,3} 2.6 Hz) and H-6e at δ 2.55 as a doubled doublet (J_{6e,6a} 14.0 Hz and J_{6e,5} 2.5 Hz). The signal for H-4 was at 2.25 as a triplet (J_{3,4} = J_{4,5} 10.8 Hz), which indicated the three substituents at C-3, C-4 and C-5 all to be in equatorial positions and the adduct 162b to be an exo-addition
product. In the $^{13}$C-NMR spectrum of adduct 162b, the peak at $\delta$ 207.51 demonstrated the existence of the ketone carbonyl group in the product.

As shown in Scheme 46, the central cyclohexaneone ring of the cycloaddition products 160, 161 and 155 is numbered clockwise having the carbonyl carbon in position 1. The central cyclohexaneone ring of the cycloaddition adducts 162a and 162b is numbered so as to make the (2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)methyl group located at C-3 and (2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-$\alpha$-D-glucopyranosyl)methyl group located at C-5. As shown in Scheme 47, the cyclohexaneone ring of the diastereomer 163 is numbered clockwise and that of the diastereomer 164 is numbered anticlockwise, both having the carbonyl group in position 1. The chemical shifts and coupling constants of hydrogens in the cyclohexaneone ring of compounds 160, 161, 155, 162a and 162b are summarized in Tables 11 and 12. The chemical shift of H-6e in compounds 160, 161 and 155 is more downfield than H-2e, which should result from the influence of the oxygen atom at C-5 in the sugar ring. The conformational behavior of compound 155 has been discussed previously. The two-dimensional proton ROESY spectrum of compound 155 demonstrated that conformer 155A was the preferred conformer. The structure of conformer 155A clearly showed that H-6e is close to the sugar ring oxygen and shows a downfield chemical shift because of the electron-withdrawing effect of the oxygen. H-2e does not experience such an influence and has its chemical shift more upfield relative to H-6e. The pattern of $^1$H-NMR spectra of compounds 160 and 161 is very similar to the $^1$H-NMR spectrum of compound 155, suggesting that they have similar conformational behavior in solution. The pattern of the $^1$H-NMR spectrum of adduct 162a is also quite similar to that of compound 155, with the chemical shift of H-6e more
downfield than that of H-2e, suggesting that the central cyclohexanone ring of compound 162a may be numbered clockwise and compound 162a has the same absolute configuration as diastereomer 163, and they are the same compound. In the $^1$H-NMR spectrum of adduct 162b, the chemical shift of H-2e is more downfield than that of H-6e, and the relative locations of signals for H-3 and H-5, as well as H-7 and H-7' are exchanged when comparison with those in compounds 162a and 155, which may suggest that the central cyclohexanone ring of compound 162b be numbered anticlockwise and compound 162b should have the same absolute configuration as diastereomer 164, and they should be the same compound.
D. Conclusions

A carbon–carbon bond has been stereoselectively introduced at the anomeric center of the activated 2-amino-2-deoxy-D-glycopyranosyl derivatives via a free-radical mechanism. The stereoselectivity is controlled by the substituents at C-2. The acetyl, trifluoroacetyl and p-methoxybenzylidene protecting groups on 2-amino function afford an α-allylation product through the allylstanne free-radical reaction with the activated 2-amino-2-deoxy-D-glycosyl derivative, whereas the large and rigid phthalimido function provides an β-allylation product. The stereoselectivity at the anomeric center during the free-radical allylation reaction is not influenced by the configuration of the substituent at the anomeric center. The rate of the free-radical reaction is controlled by both protecting groups on the 2-amino function and substituents at the anomeric center. The α-C-allylated glycopyranosyl compounds exist in a rapid equilibrium between the $^4C_1$ and $^1C_4$ conformers in solutions, and the $^1C_4$ conformer is stabilized by the intramolecular hydrogen bonding between the hydrogen atom at the amino function and the oxygen atom in the tetrahydropyran ring.

The α-C-allylated D-glucopyranosyl compound has been achieved in high yield and high stereoselectivity by chosen suitable reaction conditions. The low temperature, the solvent, and the addition rates of the Lewis acid and the allyltrimethylsilane reagent are the key factors in producing the α-allylation product in high yields and high stereoselectivity.

Six C-linked sugar dienophiles and one C-linked sugar diene have been successfully synthesized from D-glucosamine and D-glucose. In the Diels–Alder reaction of the C-linked glycosyl dienophiles with (E)-1-methoxy-3-
(trimethylsilyloxy)-1,3-butadiene, the exo-addition is much more favored than the endo-addition, and the facial selectivities in both additions are relatively low. It is concluded that the remote sugar moiety has a relatively small influence on the diastereofacial selectivity. The cyclization reaction of C-linked glycosyl dienophiles with the C-linked glycosyl diene give exclusively exo-addition products, and five C-linked pseudo-trisaccharides have been obtained in crystalline forms. The modification of the central ring in the diastereomeric pure pseudo-trisaccharide to 2-deoxystreptamine will provide the C-analogue of Kanamicins as shown in scheme 49.
C-analogue of Kanamicins

Scheme 49
Table 11. $^1$H-NMR chemical shifts (δ) and multiplicities of some important hydrogens from compounds 160$^a$, 161$^b$, 155$^a$, 162$^a$ and 162$^b$.

<table>
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<th>Compd</th>
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<th>H-3</th>
<th>H-4</th>
<th>H-5</th>
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$^a$At 500 MHz in C$_6$D$_6$. $^b$At 500 MHz in CDCl$_3$. 
Table 12. The first-order $^1\text{H}$-$^1\text{H}$ coupling constants (Hz) of some important hydrogens from compounds 160$^a$, 161$^b$, 155$^a$, 162a$^a$, and 162b$^a$.

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<th>$J_{4,5}$</th>
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$^a$At 500 MHz in C$_6$D$_6$. $^b$At 500 MHz in CDC$_3$. 
Figure 51. $^{1}$H-NMR spectrum of (3S, 4S, 5R)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-3-methoxy-4-nitrocyclohexanone (144)
Figure 52. $^{13}$C-NMR spectrum of (3S, 4S, 5R)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-3-methoxy-4-nitrocyclohexanone (144)
Figure 53. $^1$H-$^1$H ROESY spectrum of (3S, 4S, 5R)-5-(2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-glucopyranosyl)-3-methoxy-4-nitrocyclohexanone (144)
Figure 54. $^1$H-NMR spectrum of methyl 5-(2-acetamido-3,4,6-tri-O-acetyl-α-D-glucopyranosyl)-3-methoxy-1-cyclohexanone-4-carboxylate (156 or 157)

mp 183–184 °C
$[\alpha]_D +29^\circ$
mp 183–184 °C
$[\alpha]_D +29^\circ$°

Figure 55. $^{13}$C-NMR spectrum of methyl 5-(2-acetamido-3,4,6-tri-O-acetyl-α-D-glucopyranosyl)-3-methoxy-1-cyclohexanone-4-carboxylate (156 or 157)
Figure 56. $^1$H-NMR spectrum of methyl 5-(2-acetamido-3,4,6-tri-O-acetyl-$\alpha$-D-glucopyranosyl)-3-methoxy-1-cyclohexanone-4-carboxylate (157 or 156)
Figure 57. $^{13}$C-NMR spectrum of methyl 5-(2-acetamido-3,4,6-tri-O-acetyl-α-D-glucopyranosyl)-3-methoxy-1-cyclohexanone-4-carboxylate (157 or 156)
Figure 58. $^1$H-NMR spectrum of (3S, 5R)-3,5-bis(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-4-nitro-1-cyclohexanone (155)
Figure 59. $^{13}$C-NMR spectrum of (3S, 5R)-3,5-bis(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-4-nitro-1-cyclohexanone (155)
Figure 60. $^1$H-$^1$H ROESY spectrum of (3S, 5R)-3,5-bis(2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-glucopyranosyl)-4-nitro-1-cyclohexanone (155)
Figure 61. $^1$H-NMR spectrum of methyl (3S, 5R)-3,5-bis(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-cyclohexanone-4-carboxylate (160)
Figure 62. $^{13}$C-NMR spectrum of methyl (3$S$, 5$R$)-3,5-bis(2,3,4,6-tetra-$O$-benzyl-$\alpha$-D-glucopyranosyl)-1-cyclohexanone-4-carboxylate (160)
Figure 63. $^1$H-NMR spectrum of $(3S, 5R)$-3,5-bis(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-4-acetyl-1-cyclohexanone (161)
Figure 64. $^{13}$C-NMR spectrum of (3S, 5R)-3,5-bis(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-4-acetyl-1-cyclohexanone (161)
Figure 65. $^1$H-NMR spectrum of methyl (3S, 4S, 5R)-5-(2-acetamido-3,4,6-tri-$O$-acetyl-$\alpha$-$D$-glucopyranosyl)-3-(2,3,4,6-tetra-$O$-benzyl-$\alpha$-$D$-glucopyranosyl)-1-cyclohexanone-4-carboxylate (163)
Figure 66. $^{13}$C-NMR spectrum of methyl $(3S, 4S, 5R)-5$-(2-acetamido-3,4,6-tri-$O$-acetyl-$\alpha$-D-glucopyranosyl)-3-(2,3,4,6-tetra-$O$-benzyl-$\alpha$-D-glucopyranosyl)-1-cyclohexanone-4-carboxylate (163)
Figure 67. $^1$H-NMR spectrum of methyl (3$R$, 4$R$, 5$S$)-5-(2-acetamido-3,4,6-tri-$O$-acetyl-$\alpha$-$D$-glucopyranosyl)-3-(2,3,4,6-tetra-$O$-benzyl-$\alpha$-$D$-glucopyranosyl)-1-cyclohexanone-4-carboxylate (164)
mp 164-166 °C
[α]D +71°

Figure 68. $^{13}$C-NMR spectrum of methyl $(3R, 4R, 5S)-5-(2$-acetamido$-3,4,6$-tri-$O$-acetyl-$\alpha$-$D$-glucopyranosyl)$-3-(2,3,4,6$-tetra-$O$-benzyl-$\alpha$-$D$-glucopyranosyl)$-1$-cyclohexanone$-4$-carboxylate (164)
CHAPTER IV

EXPERIMENTAL

General methods. — Evaporations were conducted under diminished pressure. Reaction solvents were purified and dried by distillation as recommended. TLC was performed on precoated plates of Silica Gel 60F-254 (E. Merck); components were detected by U.V. light and by spraying the plates with 10% sulfuric acid and subsequent heating. Flash-column chromatography was performed on 230–240 mesh silica gel (E. Merck). Melting points were determined in open glass capillaries in a Thomas–Hoover apparatus, and are uncorrected. Specific rotations were determined with a Perkin–Elmer Model 241MC polarimeter at 20° unless otherwise noted. $^1$H-NMR and $^{13}$C-NMR spectra were recorded with Bruker AM-250 (250 MHz $^1$H, 62.5 MHz $^{13}$C), WM-300 (300 MHz $^1$H, 75.5 MHz $^{13}$C) and AM-500 (500 MHz $^1$H, 125 MHz $^{13}$C) spectrometers. Chemical shifts (p.p.m.) are relative to Me$_4$Si as the internal standard. Splitting patterns are designated: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Spectra with the AM-500 instrument at The Ohio State University Instrument Center were recorded by Dr. C. E. Cottrell. All signal assignments were verified by $^1$H-$^1$H and $^{13}$C-$^1$H correlation spectra. Fast-atom-bombardment (f.a.b.) mass spectra were recorded at The Ohio State University Instrument Center with Kratos VG 70-250S mass spectrometers by D.
Preparation of 2-acetamido-2-deoxy-D-glucopyranose (91). — Compound 91 was prepared by the method of Horton. Sodium (5.75 g, 0.25 mol) was added in small pieces to methanol (250 mL) in a 500-mL Erlenmeyer flask which was cooled in ice. When all the sodium had dissolved, the solution was brought to room temperature, and powdered 2-amino-2-deoxy-D-glucopyranose hydrochloride 90 (55 g, 0.255 mmol) was added. The mixture was gently swirled with thorough mixing for 3–4 min, then filtered, and the solid washed with 50-mL portions of methanol. The combined filtrate was treated without delay with acetic anhydride (30 mL, 0.31 mmol), and the stoppered flask was cooled under a running tap for a few minutes to moderate the initiate reaction. After 10 min, white crystalline product began to separate. The mixture was set aside at room temperature overnight. The product 91 was collected and washed with ether, dried by suction and then in a vacuum desiccator. A white powdery product was obtained that weighed 50.5 g (91%).

Preparation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride (92). — The chloride 92 was prepared by the procedure of Horton. In a 250-mL round-bottomed flask equipped with a magnetic stirrer bar and a reflux condenser protected by a tube of calcium chloride was placed acetyl chloride (40 mL). 2-Acetamido-2-deoxy-D-glucopyranose (91) was mixed with the acetyl chloride under good stirring at room temperature for 48 h. The reaction was vigorous during the first hour. A clear viscous, amber liquid remained at the end of the reaction. The viscous
solution was diluted with dichloromethane (600 mL), washed with ice-water twice and cold sat. NaHCO₃ twice, dried over Na₂SO₄ for 15 min, and filtered. The solution was concentrated on a rotary evaporator at 50 °C to about 15 mL, and then anhydrous diethyl ether (100 mL) was added rapidly to the concentrated residue. A clear solution was obtained and crystallization began after about 30 sec. The flask was stoppered and set aside at room temperature overnight. A white solid product was collected and dried under vacuum; it weighed 13.8 g (73%), mp 120-121 °C. The white solid product was dissolved in dichloromethane (10 mL) and then to the solution was added anhydrous diethyl ether. After keeping overnight, a white crystalline product was obtained, mp 126-127 °C; lit. 127-128 °C. ¹H-NMR data (300 MHz, CDCl₃): δ 6.19 (d, 1H, J₂₃ 3.7 Hz, H-1), 5.83 (d, 1H, J₂,₃NH 8.6 Hz, N-H), 5.33 (dd, 1H, J₂,₃ 10.7 Hz, J₃,₄ 9.3 Hz, H-3), 5.21 (dd, 1H, J₄,₅ 10.0 Hz, H-4), 4.52 (ddd, 1H, H-2), 4.27 (m, 2H, H-5 and H-6a), 4.14 (d, 1H, J₆a,₆b 10.4 Hz, H-6b), 2.10, 2.06, 2.05 and 1.99 (4s, 4×3H, 4COC₃H₃).

Preparation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl bromide (94). — This procedure is a modification of the method of Osawa. To a 30 wt. % solution of HBr in acetic acid (20 mL) was added 2-acetamido-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-glucopyranose (2.00 g, 5.14 mmol) at 0 °C. The reaction solution was stirred at 0 °C–room temperature overnight and then diluted with dichloromethane (100 mL). The solution was washed with ice-water (100 mL), cold sat. NaHCO₃ (2X100 mL) and brine (50 mL), and then dried over Na₂SO₄ in refrigerator. TLC showed the completely disappearance of the starting material (Rf 0.38, EtOAc) and one single spot for the product 94 (Rf 0.63, EtOAc). The mixture was filtered and the filtrate
evaporated to give a white solid product 94 (1.89 g, 90%), which was used without further purification.

Synthesis of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (95).

(a) From 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride. — A suspension solution of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl chloride (92, 10.97 g, 30 mmol), allyltributyltin (29 mL, 91 mmol) and AIBN (738 mg, 4.5 mmol) in dry toluene (60 mL) was degassed for 1 h and the mixture was then stirred at 85 °C under Ar. A clear solution was obtained during the first hour of heating. After 8 h of reaction, TLC showed the complete absence of starting material (Rf 0.64, EtOAc) and the presence of three new spots with Rf 0.49, 0.46, and 0.08 (EtOAc). The toluene solvent was evaporated off and the residue was dissolved in MeCN. The solution was washed three times with pentane and evaporated to give a light-yellow syrup, which was chromatographed on a column of silica gel, eluting with 4:1 EtOAc–hexanes to give the product 95 (Rp 0.49, EtOAc) as a white solid (7.46 g, 67%). This solid was crystallized from 1:3 EtOAc–hexanes, and further recrystallization afforded the pure product 95 as needles having mp 109–110 °C, [α]D +47° (c 1.2, CHCl3); NMR data see Tables 6–8; MS: m/z 372 (M + H)+, 330 (M - allyl)+, 312 (M + H - HOAc)+, 270 (M - HOAc - allyl)+.


Evaporation of the mother liquor from the recrystallization gave a syrup, which was demonstrated by its 1H-NMR spectrum to be a mixture of 95 and its β-anomer. A total of 0.22 g of the β-anomer of 95 existed in the mother liquor.
(2% yield), which had the same Rf value as 95. It was not found possible to obtain the β-anomer of 95 pure through chromatography and recrystallization. 

$^1$H-NMR data of the β-anomer of 95 (300 MHz, C$_6$D$_6$): δ 5.93 (tdd, 1H, J$_{1a,2}$ 10.3 Hz, J$_{2,3a} = J_{2,3b}$ 6.9 Hz, H-2), 5.24 (dd, 1H, J$_{3',4'}$ 9.4 Hz, J$_{4',5'}$ 9.8 Hz, H-4'), 5.19 (d, 1H, J$_{N,H,2}$ 10.5 Hz, N-H), 5.12 (dd, 1H, J$_{2',3'}$ 9.2 Hz, H-3'), 5.09 (d, 1H, H-1a), 5.06 (d, 1H, H-1b), 4.34 (dd, 1H, J$_{5',6'a}$ 4.9 Hz, J$_{6'a,6'b}$ 12.2 Hz, H-6'a), 4.16 (m, 2H, H-2' and H-6'b), 3.51 (ddd, 1H, J$_{5',6'b}$ 2.3 Hz, H-5'), 3.16 (ddd, 1H, J$_{1',2'}$ 10.1 Hz, J$_{1',3a}$ 3.8 Hz, J$_{1',3b}$ 7.4 Hz, H-1'), 2.32 (m, 2H, H-3a and H-3b), 1.74, 1.73, 1.71 and 1.63 (4s, 4×3H, 4-COCH$_3$).

The oxazoline side-product 96 (Rf 0.46, EtOAc) was obtained as a syrup (0.49 g, 5%), [α]$_D$ +13° (c 1.3, CHCl$_3$); lit. syrups, [α]$_D$ +12° (c 1.0, CHCl$_3$). The fraction having Rf 0.08 (EtOAc) was evaporated to a white solid, which was demonstrated by its mass spectrum to be an oligomeric mixture (2.69 g, 24%), MS: m/z 1114 (3M + H)$^+$, 743 (2M + H)$^+$ (M: molecular mass of compound 95).

(b) From 2-acetamido-3,4,6-tri-0-acetyl-2-deoxy-$\beta$-D-glucopyranosyl ethylxanthate (97). — A suspension solution of 2-acetamido-3,4,6-tri-0-acetyl-2-deoxy-$\beta$-D-glucopyranosyl ethylxanthate$^{88}$ (903.0 mg, 2.00 mmol), allyltributyltin (1.24 mL, 4.00 mmol), and AIBN (49.3 mg, 0.30 mmol) in dry toluene (4 mL) was degassed for 10 min. The mixture was stirred for 24 h at 80 °C under argon. A clear solution resulted during the first hour of heating and the solvent was removed under vacuum after the reaction. The residue was dissolved in MeCN, and the solution was washed three times with pentane and evaporated to a syrup, which was chromatographed on a column of silica gel (4:1 EtOAc–hexanes) to give 95 as a white solid (184.0 mg, 25%).

(c) From 2-acetamido-3,4,6-tri-0-acetyl-2-deoxy-$\alpha$-D-glucopyranosyl bromide (94): Preparation of 2-methyl-(2-acetamido-3,4,6-tri-0-
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acetyl-1,2-dideoxy-α-D-glucopyranono-[2,1-d]-2-oxazoline (96). — To a solution of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl bromide (94, 1.04 g, 2.52 mmol) and AIBN (62.1 mg, 0.38 mmol) in dry toluene (4 mL) and DME (2 mL) was added allyltributyltin (1.56 mL, 4.88 mmol). The solution was degassed for 10 min and then heated for 18 h at 80 °C under Ar. TLC showed a single spot (Rf 0.46, EtOAc) for the oxazoline 96. The residue was dissolved in MeCN, and the solution was washed three times with pentane, and evaporated to a syrup. The product was purified on a short column of silica gel, eluting with EtOAc to afford compound 96 as a syrup (735.6 mg, 88%), [α]D +12° (c 1.1, CHCl₃); lit.¹⁰² syrup, [α]D +12° (c 1.0, CHCl₃).

Synthesis of 3-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-1-propene (98) and 3-(2-acetamido-6-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (98a). — A solution of compound 95 (1.11 g, 3.00 mmol) in dry methanol (15 mL) was treated with 25 wt. % NaOMe in MeOH (0.03 mL) for 10 min at room temperature, and then neutralized with Amberlite IR-120 (H⁺) resin. The resin was filtered off, washed with MeOH, and the filtrate was evaporated to afford a white solid (0.73 g, 100%), Rf 0.38 (2:1 EtOAc–EtOH); mp 204–206 °C (from ethanol); [α]D +109° (c 1.0, methanol); NMR data (¹H, 300 MHz, CD₃SOCD₃): δ 7.70 (d, 1H, J₂=NH 7.6 Hz, NHAc), 5.75 (tdd, 1H, J₁a,2 10.2 Hz, J₁b,2 17.1 Hz, J₂,3a = J₂,3b 6.9 Hz, H-2), 5.05 (bd, 1H, H-1b), 4.97 (dd, 1H, J₁b,3 ~1.0 Hz, H-1a), 4.89 (d, 1H, J₄',OH 4.1 Hz, OH-4'), 4.75 (bs, 1H, OH-3'), 4.35 (l, 1H, J₆'a,OH = J₆'b,OH 5.9 Hz, OH-6'), 3.86 (td, 1H, J₁',2' = J₁,3b 4.8 Hz, J₁',3a 10.0 Hz, H-1'), 3.69 (m, 1H, J₂,3' 10.9 Hz, H-2'), 3.56 (ddd, 1H, J₅',₆'a 2.5 Hz, J₆'a,₆'b 11.5 Hz, H-6'a), 3.44 (m, 2H, H-3', H-6'b), 3.27 (m, 1H, H-5'), 3.13 (m, 1H, H-4'), 2.33 (m, 1H, H-3a), 2.11 (m, 1H, H-3b), 1.81 (s, 3H, NHCOCH₃); (¹³C,
75 MHz, CD$_3$SOCD$_3$): $\delta$ 169.16 (NHCOCH$_3$), 135.56 (C-2), 116.23 (C-1), 73.81 (C-5'), 72.36 (C-1'), 71.00 (C-3'), 70.37 (C-4'), 61.03 (C-6'), 53.11 (C-2'), 30.19 (C-3), 22.64 (NHCOCH$_3$); MS: m/z 268 (M + Na)$^+$, 246 (M + H)$^+$, 204 (M - allyl)$^+$. 

Anal. Calc. for C$_{11}$H$_{19}$NO$_5$ (245.273): C, 53.87; H, 7.81; N, 5.71. Found: C, 53.89; H, 7.76; N, 5.64.

When the deacetylation time was short, such as 2–3 min, compound 98a (R$_f$ 0.69, 2:1 EtOAc–EtOH) was found as a side product and could be isolated through a silica gel column, eluting with 2:1 EtOAc–ethanol; mp 179–180 ºC; NMR data (1H, 300 MHz, CD$_3$SOCD$_3$): $\delta$ 7.70 (d, 1H, J$_{2',NH}$ 7.8 Hz, NHAc), 5.70 (tdd, 1H, $J_{1a,2}$ 10.1 Hz, $J_{1b,2}$ 17.1 Hz, $J_{2,3a} = J_{2,3b}$ 6.9 Hz, H-2), 5.15 (d, 1H, $J_{3',OH}$ 5.8 Hz, OH-4'), 5.04 (d, 1H, H-1b), 4.99 (d, 1H, H-1a), 4.87 (d, 1H, $J_{4',OH}$ 5.2 Hz, OH-4'), 4.21 (dd, 1H, $J_{5',6'a}$ 1.9 Hz, $J_{6'a,6'b}$ 11.6 Hz, H-6'a), 4.04 (dd, 1H, $J_{5',6'b}$ 6.7 Hz, H-6'b), 3.87 (td, 1H, $J_{1',2'} = J_{1',3b}$ 5.0 Hz, $J_{1',3a}$ 10.0 Hz, H-1'), 3.72 (m, 1H, H-2'), 3.48 (m, 2H, H-3' and H-5'), 3.11 (m, 1H, H-4'), 2.32 (m, 1H, H-3a), 2.11 (m, 1H, H-3b), 1.98 (s, 3H, OCOCH$_3$), 1.82 (s, 3H, NHCOCH$_3$); (13C, 75 MHz, CD$_3$SOCD$_3$): $\delta$ 170.16 (COCH$_3$), 169.20 (NHCOCH$_3$), 135.20 (C-2), 116.35 (C-1), 72.08, 71.04, 71.00, 70.13, 63.53, 52.87 (C-2'), 30.26 (C-3), 22.63 (NHCOCH$_3$) and 20.60 (COCH$_3$); MS: m/z 310 (M + Na)$^+$, 288 (M + H)$^+$, 270 (M + H - H$_2$O)$^+$, 246 (M - allyl)$^+$, 228 (M + H - HOAc)$^+$.

Preparation of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-p-methoxybenzylideneamino-β-D-glucopyranose (99). — The procedure of Umezawa et al.$^8$ in the L series was used with slight modification. To a solution of 2-amino-2-deoxy-D-glucose hydrochloride (90) (3.21 g, 14.89 mmol) in 1 M sodium hydroxide (15 mL) was added a solution of p-anisaldehyde (1.87...
mL, 15.37 mmol) in ethanol (3.8 mL). The mixture was stirred at room
temperature for 40 min and then refrigerated overnight. The resultant white
crystalline solid was filtered off and washed with cold water and a mixture of 1:2
ethanol–ether, and then dried under vacuum overnight. The completely dried
solid intermediate, 2-p-anisylidenamino-2-deoxy-D-glucopyranose (3.88 g,
88%), was dissolved in pyridine (19 mL) without further purification. The
solution was cooled in ice bath and then acetic anhydride (10 mL) was added.
The mixture was stirred at room temperature for 24 h. The pyridine solution was
poured into ice-water and a white precipitate was formed, which was filtered off,
washed with cold water, and dried by vacuum; yield 4.68 g (77%); 1H-NMR data
(250 MHz, CDCl₃): 8 8.16 (s, 1H, N=CH), 7.65 and 6.91 (2d, 2X2H, J 8.8 Hz, p-
CH₂O–Ph–CH), 5.94 (d, 1H, J₁,₂ 8.3 Hz, H-1), 5.43 (dd, 1H, J₂,₃ 9.7 Hz, J₃,₄ 9.5
Hz, H-3), 5.14 (dd, 1H, J₄,₅ 10.0 Hz, H-4), 4.37 (dd, 1H, J₅,₆₈ 4.6 Hz, J₆₈,₆₉ 12.4
Hz, H-6a), 4.13 (dd, 1H, J₅,₆₉ 2.1 Hz, H-6b), 3.97 (ddd, 1H, H-5), 3.84 (s, 3H,
OCH₃), 3.45 (dd, 1H, H-2), 2.09, 2.03, 2.02 and 1.88 (4s, 4X3H, 4COCH₃).

Preparation of 3,4,6-tri-O-acetyl-2-p-
methoxybenzylidenamino-2-deoxy-α-D-glucopyranosyl bromide
(100). — The procedure of Umezawa et al.⁸⁹ in the L-series was adapted. To
a solution of the p-anisaldehyde protected compound 99 (1.50 g, 3.22 mmol) in
dry dichloromethane (0.7 mL) and acetic anhydride (0.1 mL) was added a 30
wt. % solution of HBr in acetic acid (3.4 mL). The solution was stirred in the dark
at room temperature for 4 h, and then diluted with dichloromethane, washed
with ice-water, and cold sat. NaHCO₃, dried over Na₂SO₄. Evaporation of the
solvent gave a white solid, which was dissolved in anhydrous diethyl ether.
Some of the precipitate could not dissolved in ether. The mixture was filtered
and the filtrate evaporated to give a light-yellow solid, which was recrystallized from 2:1 hexanes–toluene to afford crystalline compound 100 (0.98 g, 47%), mp 110 °C (dec.); lit\textsuperscript{89} for 3,4,6-tri-O-acetyl-2-p-anisylidenamino-2-deoxy-\(\alpha\)-L-glucopyranosyl bromide, mp 110–111 °C. \(1\)H-NMR data (250 MHz, CDCl\textsubscript{3}): \(\delta\)

- 8.24 (s, 1H, N=CH), 7.71 and 6.92 (2d, 2\(\times\)2H, \(J\) 8.6 Hz, \(\rho\)-CH\textsubscript{3}O-\(\rho\)-CH), 6.31 (d, 1H, \(J_{1,2}\) 3.3 Hz, H-1), 5.67 (dd, 1H, \(J_{2,3}\) 9.5 Hz, \(J_{3,4}\) 9.7 Hz, H-3), 5.21 (dd, 1H, \(J_{4,5}\) 10.0 Hz, H-4), 4.47 (ddd, 1H, \(J_{5,6a}\) 4.2 Hz, \(J_{5,6b}\) 1.9 Hz, H-5), 4.39 (dd, 1H, \(J_{6a,6b}\) 12.5 Hz, H-6a), 4.16 (dd, 1H, H-6b), 3.84 (s, 3H, OCH\textsubscript{3}), 3.58 (dd, 1H, H-2), 2.11, 2.06 and 1.88 (3s, 3\(\times\)3H, 3COCH\textsubscript{3}).

**Synthesis of 3-(3,4,6-tri-O-acetyl-2-amino-2-deoxy-\(\alpha\)-D-glucopyranosyl)-1-propene hydrochloric acid (101) and 3-(3,4,6-tri-O-acetyl-2-amino-2-deoxy-\(\alpha\)-D-glucopyranosyl)-1-propene (101a).**

- A solution of compound 100 (928 mg, 1.91 mmol), allylttributyltin (1.80 mL, 5.80 mmol), and AIBN (66.1 mg, 0.40 mmol) in dry toluene (6 mL) was degassed for 30 minutes. The mixture was heated for 9 h at 90 °C under Ar and then cooled to room temperature. To the solution was added AIBN (62.0 mg, 0.37 mmol) again. The solution was degassed for another 15 min and heated at 80 °C overnight again under Ar. The solvent was evaporated off and the residue was dissolved in MeCN. The solution was washed three times with pentane and evaporated to afford a syrup, which was dissolved in triethylamine (0.5 mL) and ethyl acetate (0.5 mL), and purified on a column of silica gel with 1:1 EtOAc–hexanes to give a light-yellow syrupy product 3-(3,4,6-tri-O-acetyl-2-deoxy-2-\(p\)-methoxybenzylidenamino-\(\alpha\)-D-glucopyranosyl)-1-propene (387 mg, 45%). The syrupy product was dissolved in acetone (4 mL) and to the solution were added 4 drops of 6 M HCl. A white precipitate formed immediately and it
was identified to be compound 101, mp 220–222 °C (dec.); [α]D +59° (c 0.53, methanol); NMR data see Tables 6–7; MS: m/z 330 (M - Cl)+, 288 (M - HCl - allyl)+, 270 (M - HCl - OAc)+.


Compound 101 was suspended in dichloromethane and then washed with sat. NaHCO3 and brine, dried over Na2SO4. After filtration and evaporation, compound 101a was obtained as a syrup; for NMR data see Tables 6–7.

Preparation of 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride (102). — The modified procedure of Bergmann and Zervas90 was used to prepare compound 102. To a solution of 1,3,4,6-tetra-O-acetyl-2-p-methoxybenzylideneamino-2-deoxy-β-D-glucopyranose (99, 4.00 g, 8.59 mmol) in boiling acetone (20 mL) was added dropwise 5N HCl (3 mL). A white gel-like material was formed immediately. The solution was stirred at room temperature for 1 h. The white solid product was collected, washed with ether, and dried under vacuum. The crude product was dissolved in hot methanol (100 mL) for recrystallization. After cooling to room temperature, the flask was kept in a refrigerator overnight. A white crystalline product (1.00 g) was collected and ether was used to precipitate additional product from mother liquor. The total product weighed 2.50 g (73%).

Preparation of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranose (103). — Method a:91 To a cold solution of compound 102 (2.50 g, 6.51 mmol) in dichloromethane (25 mL) and
pyridine (2.5 mL) in ice bath was added trifluoroacetic anhydride (2.5 mL). After stirring for 20 min at room temperature, the solution was washed with ice-water twice, then dried over Na₂SO₄. After filtration, the solution was concentrated to low volume (about 5 mL) and then diethyl ether was added to produce a white crystalline precipitate. The product was collected, washed with ether, dried under vacuum; yield 2.40 g (83%), mp 165-167 °C, [α]D -12.4° (c 1.0, CHCl₃); lit⁹¹ mp 167 °C, [α]D -13° (c 2.4, CHCl₃); ¹H-NMR data (250 MHz, CDCl₃): δ 7.11 (d, 1H, J₂,NH 9.6 Hz, N-H), 5.76 (d, 1H, J₁,₂ 8.7 Hz, H-1), 5.32 (dd, 1H, J₂,₃ 10.6 Hz, J₃,₄ 9.5 Hz, H-3), 5.13 (dd, 1H, J₄,₅ 9.9 Hz, H-4), 4.35 (ddd, 1H, H-2), 4.28 (dd, 1H, J₅,₆₈ 4.8 Hz, J₆₈,₆₉ 12.5 Hz, H-6a), 4.16 (dd, 1H, J₅,₆₉ 2.3 Hz, H-6b), 3.90 (ddd, 1H, H-5), 2.12, 2.10, 2.07 and 2.06 (4s, 4X3H, 4COCH₃).

Method b:⁹² 2-Amino-2-deoxy-D-glucose hydrochloride (90, 10.0 g, 46.4 mmol) was suspended in anhydrous methanol (50 mL) and then a freshly made solution of sodium methoxide in methanol (1.06 g of sodium in 20 mL of methanol) was added. The mixture was swirled for about 2 min and then filtered to remove NaCl. To the filtrate was added S-ethyl trifluorothioacetate (9.44 g, 59.6 mmol) and the mixture was stirred overnight at room temperature. Evaporation of the solvent gave a white solid, which was dried under vacuum overnight. Without further purification, the intermediate 2-deoxy-2-trifluoroacetamido-D-glucopyranose was dissolved in pyridine. The pyridine solution was cooled thoroughly in an ice bath and then acetic anhydride (30 mL) was added. The solution was then stirred for 48 h at 0 °C–room temperature. The solvents (pyridine and acetic anhydride) were removed by evaporation and the residue was dissolved in dichloromethane (300 mL). The solution was washed twice with 3% HCl, sat. NaHCO₃ and brine, and dried over Na₂SO₄. After filtration, the solution was decolorized with charcoal and
evaporated to give a white solid (18.39 g, 89.4%), which was a mixture of α and β anomers in the ratio of 1:0.82. It was used without further purification and separation.

**Preparation of 3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl bromide (104).** — The trifluoroacetyl-protected glucosamine derivative 103 (4.00 g, 9.02 mmol) was suspended in dichloromethane (3 mL).\textsuperscript{92} The reaction flask was cooled in an ice bath and then a 30 wt. % solution of HBr in acetic acid (3 mL) was added. The mixture was stirred at room temperature for 3 h and a clear solution was rapidly obtained. The solution was diluted with dichloromethane (300 mL), washed with ice-water, cold sat. NaHCO\textsubscript{3} (twice) and dried over Na\textsubscript{2}SO\textsubscript{4} for 15 min. Evaporation of the solvent afforded a syrup that was crystallized from 1:5 toluene–hexanes. The crystalline product was filtered off and dried under vacuum to give 104; yield 3.89 g (93%), mp 94–96°, [α]D \textsuperscript{o} +125.3° (c 1.0, CHCl\textsubscript{3}); lit.\textsuperscript{92} mp 96-97°, [α]D \textsuperscript{o} +125 ±1° (c 2.7, CHCl\textsubscript{3}); \textsuperscript{1}H-NMR data (250 MHz, CDCl\textsubscript{3}): δ 6.75 (d, 1H, J 2\textsubscript{a} = 8.2 Hz, N-H), 6.55 (d, 1H, J 1,2 = 3.7 Hz, H-1), 5.40 (dd, 1H, J 2 = 10.2 Hz, J 3,4 = 9.7 Hz, H-3), 5.27 (t, 1H, J 4,5 = 9.7 Hz, H-4), 4.31 (m, 3H, H-2, H-5 and H-6\textsubscript{a}), 4.15 (dd, 1H, J 5,6\textsubscript{b} = 1.9 Hz, J 6\textsubscript{a},6\textsubscript{b} = 12.4 Hz, H-6\textsubscript{b}), 2.11, 2.07 and 2.06 (3s, 3X3H, 3COCH\textsubscript{3}).

**Synthesis of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)-1-propene (105).** — The bromide derivative 104 (931.4 mg, 2.00 mmol), allyltributyltin (1.24 mL, 4.00 mmol), and AIBN (57.8 mg, 0.35 mmol) in dry toluene (6 mL) was degassed for 15 min and the mixture was then heated for 6 h at 80–85° C under Ar. The
solvent was evaporated off and the residue was dissolved in MeCN. The solution was washed three times with pentane and evaporated to give a light-yellow syrup, which was purified on a column of silica gel that was eluted with 1:2 EtOAc–hexanes to afford a mixture of the α, β anomers of 105 as a colorless syrup (559.4 mg, 65%, α:β = 12:1). The mixture was dissolved in hot 1:4 EtOAc–hexanes, and then an early precipitated syrup was collected, which was pure 105, Rf 0.52 (1:1 EtOAc–hexanes); [α]D +22° (c 1.1, CHCl3); NMR data see Tables 6–7; MS: m/z 426 (M + H)+, 384 (M - allyl)+, 366 (M - OAc)+, 324 (M - HOAc - allyl)+, 306 (M + H - 2HOAc)+, 264 (M - 2HOAc - allyl)+.


**Preparation of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (106).** — Compound 106 was prepared by a modification of the procedure of Lemieux.93 D-Glucosamine hydrochloride (21.6 g, 100 mmol) was added to a solution of sodium methoxide (prepared from 2.3 g of sodium in 100 mL of methanol). After shaking for 10 min, the separated sodium chloride salt was removed by filtration and washed with methanol (50 mL). The combined filtrate were treated with finely ground phthalic anhydride (7.4 g, 50 mmol) and shaken for 10 min. Triethylamine (10.1 g, 100 mmol) was then added and the clear solution was treated with phthalic anhydride (8.1 g, 55 mmol). After shaking for 10 min, a crystalline solid started to precipitate. The mixture was then brought to 50 °C and stirred for 20 min. After being kept at 0 °C for 1 h, the solid was collected by filtration, washed with diethyl ether and dried under vacuum; yield 20.8 g. The completely dried reaction intermediate was treated with pyridine (100 mL) and acetic anhydride
(50 mL) at room temperature for 24 h. The solution was poured into ice–water and the aqueous mixture was subsequently extracted with dichloromethane (3X100 mL). The combined extracts were washed successively with cold water, 3% HCl, sat. NaHCO₃ and water, and dried over Na₂SO₄. Evaporation of the solvent gave a yellow solid that was dissolved in ethyl acetate (300 mL) and the solution was decolored with charcoal. The solvent was removed to afford a light-yellow solid, which was recrystallized from diisopropyl ether to give a white crystalline solid (20.2 g, 42%), mp 90–95 °C. The ¹H-NMR spectrum showed it to be a mixture of α and β-anomers in the ratio of 1:8; lit. for pure β anomer, mp 91–94°. ¹H-NMR data of compound 106 (250 MHz, CDCl₃): δ 7.87–7.70 (m, 4H, Phth), 6.48 (d, 1H, J₁,₂ 8.9 Hz, H-1), 5.86 (dd, 1H, J₂,₃ 10.6 Hz, J₃,₄ 9.1 Hz, H-3), 5.18 (dd, 1H, J₄,₅ 10.1 Hz, H-4), 4.44 (dd, 1H, H-2), 4.34 (dd, 1H, J₅,₆a 4.4 Hz, J₅a,₆b 12.5 Hz, H-6a), 4.12 (dd, 1H, J₅,₆b 2.2 Hz, H-6b), 4.00 (ddd, 1H, H-5), 2.08, 2.01, 1.96 and 1.83 (4s, 4X3H, 4COCH₃).

Preparation of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide (107). — To a solution of compound 106 (9.54 g, 0.02 mol) in acetic anhydride (5 mL) was added 30 wt. % solution of HBr in glacial acetic acid. The solution was stirred at room temperature for 24 h, diluted with dichloromethane (200 mL), washed with ice-water and cold sat. NaHCO₃, and dried over Na₂SO₄ for 10 min. Evaporation of the solvent left a yellow solid, which was recrystallized from diisopropyl ether (100 mL) to give a light-yellow solid (6.5 g, 65%), mp 119–123 °C; lit. for compound 107, mp 122–123 °C. The ¹H-NMR spectrum showed the product to be a mixture of α and β-anomers in the ratio of 1:5. The product was used without further purification and separation. ¹H-NMR data of compound 107 (250 MHz,
Preparation of 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (108). — The chloride derivative 108 was prepared by the method of Akiya and Osawa.94 To a solution of the protected D-glucosamine derivative 106 (2.00 g, 4.19 mmol) in dry dichloromethane (20 mL) was added anhydrous AlCl₃ (1.5 g, 11.25 mmol). The solution was stirred at room temperature for 40 min, whereupon it became a light yellow-green color. The solution was poured into ice-water and the aqueous solution was extracted with dichloromethane (3X50 mL). The combined dichloromethane solution was dried over Na₂SO₄ for 1 h, filtered, and evaporated to a white solid, which was recrystallized from 1:2 toluene–hexanes (210 mL) to give the product as white needles (1.33 g, 70%), mp 150–151 °C; [α]₀ +62.1° (c 1.05, CHCl₃); lit.94 mp 149°C, [α]₀ +61.7° (c 1.51, CHCl₃). ¹H-NMR data for 108 (250 MHz, CDCl₃): δ 7.90–7.75 (m, 4H, Phth), 6.41 (d, 1H, J₁₂ 9.6 Hz, H-1), 5.76 (dd, 1H, J₂₃ 10.4 Hz, J₃₄ 9.1 Hz, H-3), 5.26 (dd, 1H, J₄₅ 10.3 Hz, H-4), 4.63 (dd, 1H, H-2), 4.33 (dd, 1H, J₅₆₈ 4.7 Hz, J₆₈₆₉ 12.5 Hz, H-6a), 4.20 (dd, 1H, J₅₆₉ 2.2 Hz, H-6b), 3.96 (ddd, 1H, H-5), 2.13, 2.04 and 1.87 (3s, 3X3H, 3COCH₃).

Synthesis of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-1-propene (109). (a) From compound 107. — To a solution of the bromide 107 (1.49 g, 3.00 mmol) and AIBN (73.9 mg, 0.45 mmol)
in dry toluene (6 mL) was added allyltributyltin (1.86 mL, 6.00 mmol). The solution was degassed for 15 min and then heated at 85 °C under Ar for 20 h, and then cooled to room temperature. A second portion of AIBN (74.8 mg, 0.45 mmol) was added to the solution, which was again degassed for 15 min and heated for 4 h under Ar at 90 °C. TLC showed the complete disappearance of the strongly charring spot at Rf 0.47 (1:1 EtOAc–hexanes) for the starting material, the product 109 had the same Rf value as the starting material, but showed a very light color after spraying with 10% sulfuric acid and subsequent heating, and another new spot at Rf 0.29. The toluene solvent was evaporated and the residue was dissolved in MeCN. The solution was washed three times with pentane and evaporated to afford a syrup. The syrup was purified on a column of silica gel, eluting with 1:1 EtOAc–hexanes to give compound 109 as a white solid (543.1 mg, 40%), which crystallized from 1:3 EtOAc–hexanes, mp 79–81 °C; [α]D +70° (c 1.2, CHCl3); The 1H-NMR spectrum showed that the white crystalline product co-existed with solvents EtOAc and hexanes in the ratio of 1:0.25:0.20, which was very stable in air. The co-existing solvents were removed at 50 °C under vacuum to afford a pure glassy product 109. NMR data see Tables 6–7; MS: m/z 460 (M + H)+, 418 (M - allyl)+, 400 (M - OAc)+, 358 (M - HOAc - allyl)+, 340 (M + H - 2HOAc)+, 298 (M - 2HOAc - allyl)+, 280 (M + H - 3HOAc)+.

Anal. Calc. for C23H25NO9 (459.448): C, 60.13; H, 5.48; N, 3.05. Found: C, 60.02; H, 5.56; N, 3.10.

The second fraction (Rf 0.29, 1:1 EtOAc–hexanes) was evaporated to a syrup, which was indicated by 1H-NMR to be a mixture of elimination product glycal 110 (16%) and a product of reduction 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-2-phthalimido-D-glucitol (111) (8%). After recrystallization from 1:4
EtOAc–hexanes, 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-2-phthalimido-D-
arabino-hex-1-enitol (110) was obtained as colorless needles, mp 126–127
°C; [α]D -11° (c 0.57, CHCl3); lit.95 syrup, [α]D -15° (c 0.20); 1H-NMR data for
110 (300 MHz, C6D6): δ 7.44, 6.83 (m, 4H, Phth), 6.44 (s, 1H, H-1), 5.95 (d, 1H,
J3,4 4.0 Hz, H-3), 5.36 (dd, 1H, J4,5 4.7 Hz, H-4), 4.48 (dd, 1H, J5,6a 6.4 Hz,
J6a,6b 11.8 Hz, H-6a), 4.27 (m, 1H, H-5), 4.20 (dd, 1H, J5,6b 3.8 Hz, H-6b), 1.65,
1.62, 1.47 (3s, 3x3H, 3OAc); 1H-NMR data for 111 (300 MHz, C6D6): δ7.43,
6.87 (m, 4H, Phth), 6.06 (dd, 1H, J2,3 10.4 Hz, J3,4 9.1 Hz, H-3), 5.28 (dd, 1H,
J4,5 10.1 Hz, H-4), 4.63 (ddd, 1H, J1a,2 11.4 Hz, J1e,2 5.5 Hz, H-2), 4.26 (t, 1H,
J1a,1e 11.2 Hz, H-1a), 4.25 (dd, 1H, J5,6a 4.6 Hz, J6a,6b 12.3 Hz, H-6a), 4.05 (dd,
1H, J5,6b 2.1 Hz, H-6b), 3.56 (dd, 1H, H-1e), 3.35 (ddd, 1H, H-5), 1.70, 1.61 and
1.44 (3s, 3OAc).

(b) Attempted C-allylation of compound 108. The same reaction
conditions as used for the free radical reaction of compound 107 with
allyltributytin initiated with AIBN in toluene solvent were used with compound
108. However, no product 109 was detected in the product mixture.

Preparation of 2-acetamido-2-deoxy-D-galactopyranose (113).
— To a solution of sodium methoxide in methanol (574.8 mg of sodium in 25 mL
of methanol) was added D-galactosamine hydrochloride (5.39 g, 25.0 mmol).
After swirling for 1 min, the NaCl salt was filtered off and to the filtrate was
added immediately acetic anhydride (3 mL). The solution was swirled for 10
min, and then refrigerated overnight. The solution was cloudy and was treated
with diethyl ether to precipitate more product. The product was filtered, washed
with diethyl ether and dried by vacuum. Compound 105 weighed 5.56 g
(100%) and appeared as an α,β-mixture.
Preparation of 2-acetamido-1,3,4,6-tetra-O-acetyl-2-deoxy-D-galactopyranose (114). — A solution of D-galactosamine hydrochloride (2.00 g, 9.28 mmol) in a mixture of pyridine (15 mL) and acetic anhydride (10 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (300 mL) and washed with ice-water, 3% HCl twice, sat. NaHCO₃ and water, dried over Na₂SO₄. The solvent was removed in vacuo to give a syrup, which crystallized upon addition of a small amount of absolute ethanol. The crystalline product (552.5 mg) collected proved to be the pure β-anomer, mp 233–234 °C; lit. mp 235 °C. The mother liquid was concentrated, charged to a silica gel column and eluted with EtOAc. Pure α-anomer (671.2 mg) was obtained, mp 176–178 °C; lit. mp 178 °C. A mixture of α and β-products (1.2163 g) was also isolated. The total product weighed 2.44 g (68%). NMR data for 2-acetamido-1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-galactopyranose (¹H, 300 MHz, CDCl₃): δ 6.23 (d, 1H, J₁,₂ 3.6 Hz, H-1), 5.64 (d, 1H, J₂,NH 9.1 Hz, N-H), 5.43 (dd, 1H, J₃,₄ 3.2 Hz, J₄,₅ 2.1 Hz, H-4), 5.22 (dd, 1H, J₂,₃ 11.6 Hz, H-3), 4.71 (ddd, 1H, H-2), 4.26 (dt, 1H, J₅,₆a = J₅,₆b 6.7 Hz, H-5), 4.09 (m, 2H, H-6a and H-6b), 2.18 (s, 6H, 2COCH₃), 2.03, 2.02 and 1.95 (3s, 3X3H, 3COCH₃); (¹³C, 75.5 MHz, CDCl₃): δ170.92, 170.19, 170.04, 169.98 and 168.68 (5C=O), 91.18 (C-1), 68.42, 67.68, 66.60, 61.17 (C-3, C-4, C-5 and C-6), 46.85 (C-2), 22.93 (NHCOH₃), 20.74, 20.54, 20.48 and 20.45 (4O₂CCH₃).

(1.47g, 6.65 mmol) was suspended in acetyl chloride (5 mL), and the mixture was stirred at room temperature for 24 h under reflux. At the end of the reaction, the mixture was a clear pink-red solution. The solution was diluted with dichloromethane (100 mL), washed with ice-water and cold sat. NaHCO3, dried over Na2SO4 for 10 min, and filtered. The solution was evaporated to a small volume (~2 mL), and then diethyl ether (100 mL) was added to afford a clear solution. Hexanes was added until the solution was slightly cloudy. The solution was kept in refrigerator overnight and some deep colored material precipitated. The mixture was filtered and the filtrate evaporated to give a light-yellow foamy solid (1.29 g), whose 1H-NMR spectrum showed it to be a mixture of the desired product 115 (697.3 mg, 29%) and 2-methyl-(2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-galactopyrano)-[2,1-d]-2-oxazoline 116 (593.4 mg) in the ratio of 1:0.85.

**Method b:** A solution of 2-acetamido-1,3,4,6-tetra-O-acetyl-2-deoxy-β-D-galactopyranose (1.00 g, 2.57 mmol) in dry dichloromethane (40 mL) was treated with 1 M TiCl4 in CH2Cl2 (4.5 mL). A solid complex was formed immediately. The mixture was refluxed for 4 days, and then cooled to room temperature, diluted with dichloromethane (200 mL), washed with ice-water, and cold NaHCO3. The solution was dried over Na2SO4 for 15 min, filtered and evaporated to give a yellow solid (829.5 mg, 88%), whose 1H-NMR spectrum showed it to be the pure α-anomer. NMR data (1H, 300 MHz, CDCl3): δ 6.27 (d, 1H, J1,2 3.7 Hz, H-1), 5.68 (d, 1H, J2,NH 8.8 Hz, N-H), 5.47 (dd, 1H, J3,4 3.2 Hz, J4,5 1.2 Hz, H-4), 5.29 (dd, 1H, J2,3 11.3 Hz, H-3), 4.79 (ddd, 1H, 1H, H-2), 4.49 (ddd, 1H, J3,6 11.3 Hz, H-6a), 4.09 (dd, 1H, H-6b), 2.17, 2.06, 2.03 and 2.00 (4s, 4x3H, 4COCH3); (13C, 75.5 MHz, CDCl3): 8 170.74, 170.19, 170.08, and 169.84 (4C=O), 94.88 (C-1), 69.84,
67.32, 66.50, 61.00 (C-3, C-4, C-5 and C-6), 49.25 (C-2), 23.06 (NHCONH), 20.52 and 20.47 (s02CCCH3).

If the starting material used was the α and β mixture of 114, the same reaction conditions produced a mixture of compound 115 (617.8 mg, 66%) and the oxazoline product 116 (225.6 mg), as determined with 1H-NMR spectrum of the mixture.

**Synthesis of 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl)-1-propene (117).** — To a solution of the mixture of 2-amino-2-deoxy-D-galacopyranosyl chloride derivative 115 and oxazoline 116 (1.2456 g, 1:0.85 by 1H NMR spectrum, 1.93 mmol of 115) in dry toluene (7 mL) were added allyltributyltin (3.27 mL, 10.7 mmol) and AIBN (87.4 mg, 0.53 mmol). The solution was degassed for 30 min and then heated for 7 h at 85 °C under Ar. The toluene solvent was removed and the residue was dissolved in CH3CN. The solution was washed three times with pentane and evaporated to a syrup, which was chromatographed on a column of silica gel with 4:1 EtOAc–hexanes to afford a mixture of product 117 and oxazoline 116. To a solution of the mixture in acetone (20 mL) was added a 1% aqueous solution of HCl (1 mL) to convert the oxazoline 116 into the more-polar compound 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-α-D-galactopyranose hydrochloride for easy separation. The solvent was evaporated after 24 h, and the residue was dissolved in dichloromethane. The solution was washed with sat. NaHCO3, brine, dried (Na2SO4) and evaporated to a syrup, which was chromatographed on a column of silica gel with 4:1 EtOAc–hexanes to give 117 as a white solid (293.5 mg, 56%), Rf 0.39 (EtOAc); mp 129–130 °C (from 1:2 EtOAc–hexanes);
$[\alpha]_D +81^\circ$ (c 1.0, CHCl$_3$); NMR data see Tables 6–7; MS: $m/z$ 372 ($M + H$)$^+$, 330 ($M$ - allyl)$^+$, 312 ($M$ - OAc)$^+$, 270 ($M$ - HOAc - allyl)$^+$, 252 ($M + H - 2$HOAc)$^+$.

Anal. Calc. for C$_{17}$H$_{25}$NO$_8$: C, 54.98; H, 6.79; N, 3.77. Found: C, 54.90; H, 6.76; N, 3.75.

**Preparation of 2-acetamido-1,3,4,6-tetra-O-acetyl-2-deoxy-$\alpha$-D-mannopyranose (118).** — A solution of $\alpha$-mannosamine hydrochloride (2.00 g, 9.28 mmol) in a mixture of pyridine (15 mL) and acetic anhydride (10 mL) was stirred at room temperature overnight. The mixture was diluted with dichloromethane (300 mL) and washed with ice-water, 3% HCl twice, sat. NaHCO$_3$ and water, dried over Na$_2$SO$_4$. The solvent was removed in vacuo to give a white solid, which was recrystallized from ethanol to provide a white crystalline product 118 (2.86 g, 79%), mp 158–159 °C; $[\alpha]_D -13.5^\circ$ (c 1.06, CH$_2$Cl$_2$); NMR data ($^1$H, 300 MHz, CDCl$_3$): $\delta$ 5.86 (d, 1H, $J_{1,2}$ 1.7 Hz, H-1), 5.81 (d, 1H, $J_{2,NH}$ 9.1 Hz, N-H), 5.12 (dd, 1H, $J_{3,4}$ 9.7 Hz, $J_{4,5}$ 9.3 Hz, H-4), 5.06 (dd, 1H, $J_{2,3}$ 3.8 Hz, H-3), 4.78 (ddd, 1H, $J_{5,6a}$ 5.3 Hz, $J_{5,6b}$ 2.5 Hz, H-5), 4.29 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.10 (dd, 1H, H-6b), 3.80 (ddd, 1H, H-2), 2.11, 2.10, 2.09, 2.06 and 2.01 (5s, 5X3H, 5COCH$_3$); ($^1$C, 75.5 MHz, CDCl$_3$): $\delta$ 170.42, 170.32, 169.90, 169.54 and 168.16 (5C=O), 90.60 (C-1), 73.39, 71.20, 65.25, 61.83 (C-3, C-4, C-5 and C-6), 49.43 (C-2), 23.22(NHCOCH$_3$), 20.64, 20.61, 20.56 and 20.49 (4O$_2$CCH$_3$).

**Preparation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-$\alpha$-D-mannopyranosyl chloride (119).** — $\alpha$-D-Mannosamine pentaacetate (118) (2.00 g, 5.14 mmol) was dissolved in acetic acid (30 mL) and the anhydrous HCl gas was passed through the solution for about 10 min. The
flask was stoppered and the solution was stirred for 48 h at room temperature, and then diluted with dichloromethane (250 mL). The solution was washed with ice-water, cold sat. NaHCO₃, dried over Na₂SO₄ for 10 min, filtered and evaporated to a syrup. The syrup was dissolved in diethyl ether (200 mL). To the solution was added hexanes until it became cloudy. The solution was kept in refrigerator overnight whereupon a deep-colored material precipitated. The solution was filtered and evaporated to give 119 as a foamy solid (1.00 g, 53%). NMR data (¹H, 300 MHz, CDCl₃): δ 6.07 (d, 1H, J₂,NH 8.3 Hz, N-H), 6.01 (d, 1H, J₁₂ 1.2 Hz, H-1), 5.62 (dd, 1H, J₂₃,₄ 4.6 Hz, J₃₄ 10.4 Hz, H-3), 5.18 (dd, 1H, J₄₅ 9.7 Hz, H-4), 4.75 (ddd, 1H, H-2), 4.32 (m, 2H, H-5 and H-6a), 4.09 (d, 1H, J₆₆b 10.5 Hz, H-6b), 2.11, 2.08, 2.07 and 2.01 (4s, 4X3H, 4COCH₃); (¹³C, 75.5 MHz, CDCl₃): δ 170.41, 170.12, 169.77 and 169.42 (4C=O), 89.96 (C-1), 70.75, 67.49, 65.19, 61.65 (C-3, C-4, C-5 and C-6), 53.44 (C-2), 23.13 (NHCOCH₃), 20.79, 20.63 and 20.52 (3O₂CCH₃).

Attempt to synthesize 3-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-mannopyranosyl)-1-propene: Formation of 2-methyl-(2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-β-D-mannopyranosyl)-[2,1-ß]-2-oxazoline (120). — To a solution of compound 119 (620.7 mg, 1.70 mmol) and AIBN (41.8 mg, 0.25 mmol) in dry toluene (4 mL) was added allyltributyltin (1.63 mL, 5.10 mmol). The solution was degassed for 15 min, heated for 6 h at 85 °C under Ar and evaporated. The residue was dissolved in MeCN, and the solution was washed three times with pentane, and evaporated to a syrup, which was applied to a short column of silica gel. Washing the column with ethyl acetate and evaporation gave a crystalline residue of 120 (458.0 mg,
82%). Recrystallization from ether afforded needles, mp 127-128 °C; \([\alpha]_D -31^\circ\) (c 1.0, CHCl₃); lit.¹⁰³ mp 132-133 °C; \([\alpha]_D -30^\circ\) (c 1.0, CHCl₃).

**Preparation of 2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-glucopyranose (122).** — The procedure of Glaudemans and Fletcher¹⁰⁴ was followed. Methyl \(\alpha\)-D-glucopyranoside (25 g, 0.129 mol) and potassium hydroxide (125 g, 2.228 mol) were suspended in dry 1,4-dioxane (80.0 mL). The mixture was stirred and gently boiled under reflux while benzyl chloride (120 mL, 1.043 mol) was added dropwise during 2 h. The mixture was stirred for 3 h at 105 °C and then cooled to room temperature. Water was added to dissolve the solid potassium hydroxide. The 1,4-dioxane layer was separated from the water layer, which was washed with diethyl ether. The organic solutions were combined, washed with water, dried over MgSO₄, and evaporated to a syrup. Without further purification, the crude intermediate methyl 2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-glucopyranoside (121) was dissolved in hot acetic acid (1.25 L). To the acetic acid solution was added the boiling 1 M aqueous sulfuric acid (270 mL). The solution was stirred for 4 h at 85 °C, and then a second portion of boiling sulfuric acid solution (1M, 270 mL) was added again. The solution was stirred for 4 h at 75–80 °C. To the solution was added a third portion of boiling sulfuric acid solution (2N, 270 mL) whereupon a copious white precipitate appeared. The mixture was stirred for another 12 h at 75-80 °C and then cooled to room temperature. The product crystallized from the acidic solution during cooling, and was filtered off, washed with water to neutrality, and dried in vacuo at 45 °C. Compound 122 was obtained as white crystallines (42.95g, 62%), which was recrystallized from methanol to give needle crystals, mp 152–153 °C, \([\alpha]_D +16.0^\circ\) (c 1.26, CHCl₃); lit.¹⁰⁴ mp 151–152 °C, \([\alpha]_D +21.7^\circ\) (c 2.19, CH₃Cl).
Preparation of 2,3,4,6-tetra-O-benzyl-1-O-p-nitrobenzoyl-D-glucopyranose (123). — The procedure of Glaudemans and Fletcher\textsuperscript{104} was followed with some modification. To a solution of compound 122 (32.5 g, 0.0601 mol) in dichloromethane (250 mL), p-nitrobenzoyl chloride (12.58 g, 0.0678 mol) and pyridine (7.9 mL) were added. The mixture was stirred at room temperature for 21 h, whereupon a white precipitate of pyridine hydrochloride salt was observed. TLC showed that the reaction was not complete, and so a second portion of p-nitrobenzoyl chloride (3.0 g, 0.0162 mol) and pyridine (3.8 mL) were added to the solution. The reaction was continued for another 7 h and then a third portion of p-nitrobenzoyl chloride (3.0 g, 0.0162 mol) was added. The reaction was run overnight again and then terminated by addition of chips of ice. The mixture was stirred for 2 h to decompose the unreacted p-nitrobenzoyl chloride. The solution was diluted with dichloromethane (200 mL), washed successively with water, aq. HCl (3%) and brine, dried (MgSO\textsubscript{4}) and evaporated to give a light-yellow solid, which was recrystallized from 5:2 methanol-propanol (700 mL), and then cyclohexane (700 mL) to afford a pure white solid (37.5 g, 90.5%), whose \textsuperscript{1}H-NMR spectrum showed it to be a mixture of α, β anomers (α : β 1.00: 2.73). The pure α or β anomer of compound 123 could be obtained by repeating recrystallization from isopropyl ether, and it was not necessary to use the pure α or β-anomer for the next step of the synthesis.

Preparation of 3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-propene (124). — To a solution of compound 123 (16.0 g, 23.2 mmol) in dry acetonitrile (200 mL), which had been stirred for 30 min at 0 °C, were added separately allyltrimethylsilane (28 mL, 176 mmol) and boron trifluoride etherate
(5.0 mL, 40.7 mol) through two additional funnels over a period of 15 min. A white precipitate was formed gradually. The reaction mixture was stirred for 19 h at 0 °C–room temperature. TLC showed the completely disappearance of starting material 123 (Rf 0.65, 1:1 hexanes–ether) and a formation of a single spot for the product 124 (Rf 0.71, 1:1 hexanes–ether). The solvent was removed and the residue was redissolved in dichloromethane (300 mL). The solution was washed with sat. NaHCO₃ and brine, dried with MgSO₄, and evaporated to give a light-yellow solid. A short column of silicon gel was used to remove some highly polar, colored materials in the crude product (eluting with 2:1 hexanes–ether). After evaporation of the main fraction, a white solid was obtained (12.05 g, 92%), which was recrystallized from methanol to provide needle crystals of the pure α anomer 123 (11.50 g, 88%), mp 64.0–65.5 °C; [α]D +36.5° (c 1.28, CHCl₃); lit.¹⁰⁵ [α]D +32.1° (c 0.97, CHCl₃); NMR data (¹H, 300 MHz, CDCl₃): δ 7.38–7.18 (m, 20H, 4CH₂Ph), 5.89 (ddt, 1H, J₁a,₂ 17.1 Hz, J₁b,₂ 10.2 Hz, J₂,₃a = J₂,₃b 6.9 Hz, H-2), 5.17 (d, 1H, H-1a), 5.13 (d, 1H, H-1b), 5.01–4.51 (8d, 8H, 4CH₂Ph), 4.19 (dt, 1H, J₁',₂' = J₁',₃a 5.0 Hz, J₁',₃b 9.6 Hz, H-1'), 3.89–3.65 (m, 6H, H-2', H-3', H-4', H-5', H-6'a and H-6'b), 2.56 (m, 2H, H-3a and H-3b); (¹³C, 75 MHz, CDCl₃): δ 138.75, 138.22, 138.09, 134.72 (C-2), 128.37, 128.33, 128.27, 127.90, 127.85, 127.81,127.76, 127.73, 127.65, 127.54, 127.52, 116.81 (C-1), 82.37, 80.04, 78.12, 75.35, 75.00, 76.68 (C-1'), 73.43, 73.03, 71.16, 68.97 and 29.79 (C-3); MS: m/z 565 (M + H)+, 473 (M - CH₂Ph)+, 457 (M - OCH₂Ph)+, 365 (M - HOCH₂Ph - CH₂Ph)+.


The mother liquor was evaporated and the residue (1.50 g) was analyzed by ¹H-NMR to be mixture of α,β anomers (α:β 4.88:1). The total
amount of β isomer of 124 was 0.26 g and α anomer 12.74 g. The α and β selectivity for the reaction was 98:2.

Synthesis of 2-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)ethanal (130). — To a solution of benzylated 3-(α-D-glucopyranosyl)-1-propene (124, 4.00 g, 7.1 mmol) in dry dichloromethane (200 mL) was added dry methanol (0.43 mL, 10.6 mmol). The solution was stirred at -77 °C (acetone in dry ice) for 15 min, and then O₃ gas produced by a Welsbach Laboratory Ozonator was passed through the solution until a blue color was observed. Argon gas was used to remove the blue color and to the solution was added dimethylsulfide (25 mL) through an additional funnel. The solution was stirred at -77 °C–room temperature and monitored by TLC, which showed the immediately disappearance of the starting material 124 (Rf 0.71, 1:1 hexanes–ether), one spot for the intermediate ozonide (Rf 0.55, 1:1 hexanes–ether) and one spot for the aldehyde product 130 (Rf 0.31, 1:1 hexanes–ether). After 27 h, the ozonide intermediate was almost completely reduced to the aldehyde product. The solution was washed with sat. NaHCO₃, dried over MgSO₄, filtrated and evaporated to a colorless syrup (3.44 g, 83%). In the ¹H-NMR spectrum, the signal for the aldehyde hydrogen was at δ 9.72 as a doubled doublet (J₁,₂a 1.6 Hz, J₁,₂b 2.9 Hz). The colorless syrup was used directly without further purification for conversion into compound 136.

Synthesis of 2-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)ethanal (131). — A solution of 2-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-1-propene (95, 1.00 g, 2.69 mmol) in dry dichloromethane (100 mL) was stirred at -77° for 30 min, and then O₃ gas was
passed though the solution until a blue color was observed. Argon was used to remove O₃ gas until the solution became colorless. To the solution was added dimethyl sulfide (25 mL) and the solution was stirred at -77°–room temperature for three days when it became gradually yellow. TLC showed complete disappearance of the starting material (Rf 0.55, EtOAc) and a major spot for product 131 (Rf 0.25, EtOAc). The solution was washed with sat. NaHCO₃ and brine, dried over Na₂SO₄, filtered, and the filtrate was evaporated to a syrup, which was purified on a column of silica gel, eluting with EtOAc. Evaporation of the eluate gave product 131 as a colorless solid foam (0.75 g, 75%); The ¹H-NMR spectrum showed the aldehyde hydrogen peak at δ 9.74; MS: m/z 374 (M + H)+, 356 (M + H - H₂O)+, 314 (M + H - HOAc)+. This aldehyde product 131 was used without further purification.

**Synthesis of 2-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)ethanal (132).** — A solution of 3-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)-1-propene (105, 3.40 g, 7.99 mmol) in dry dichloromethane (150 mL) was cooled at -77 °C for 15 min and then O₃ gas was passed through the solution until a blue color was observed. Argon gas was used to remove the excess of O₃ gas until the solution became colorless and then dimethyl sulfide (20 mL) was added slowly to the solution. The solution was stirred at -77 °C–room temperature for 24 h. TLC indicated complete disappearance of the starting material (Rf 0.49, 1:1 hexanes–EtOAc) and a major spot resulted for the aldehyde product 132 (Rf 0.35, 1:1 hexanes–EtOAc). The solution was washed with sat. NaHCO₃, dried over Na₂SO₄, filtered and evaporated to a syrup, which was loaded on a short silica gel column to remove the side-
product methyl sulfoxide (eluting solvent, 1:1 hexanes–EtOAc). Evaporation of the eluate gave 132 as a colorless solid foam (2.88 g, 84%), which was used for the following step reaction without further purification. NMR data (1H, 300 MHz, CDCl3): δ 9.71 (dd, 1H, J1,2b 0.85 Hz, J1,2a 2.3 Hz, H-1), 7.20 (d, 1H, JNH,2' 9.2 Hz, N-H), 5.03 (t, 1H, J2',3'=J3',4' 4.3 Hz, H-3'), 4.89 (dd, 1H, J4',5' 3.5 Hz, H-4'), 4.78 (ddd, 1H, J1',2' 2.9 Hz, J1',2a 8.9 Hz, J1',2b 4.5 Hz, H-1'), 4.62 (dd, 1H, J5',6'a 8.0 Hz, J6'a,6'b 12.0 Hz, H-6'a), 4.22 (m, 1H, H-2'), 4.19 (dd, 1H, J5',6'b 4.9 Hz, H-6'b), 4.09 (m, 1H, H-5'), 2.70 (ddd, 1H, J2a,2b 16.9 Hz, H-2a), 2.57 (ddd, 1H, H-2b), 2.17, 2.12 and 2.10 (3s, 3X3H, 3O2CCH3); MS: m/z 428 (M + H)+, 410 (M + H - H2O)+, 384 (M - CH2CHO)+, 368 (M + H - HOAc)+, 350 (M + H - HOAc - H2O)+, 308 (M + H - 2HOAc)+, 290 (M + H - 2HOAc - H2O)+.

Synthesis of methyl (E)-4-{2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl}-but-2-enoate (133). — To a solution of 2-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)ethanal (130, 3.58 g, 6.32 mmol) in dry benzene (35 mL) was added methyl (triphenylphosphoranylidene)acetate (4.22 g, 12.64 mmol). The reaction solution was refluxed for 24 h. TLC showed that there was no remaining starting material 130 (RF 0.31, 1:1 hexanes–ether), but a major product spot (RF 0.42, 1:1 hexanes–ether). The solution was cooled to room temperature, diluted with dichloromethane, washed with brine, and dried over MgSO4. After removal of MgSO4, the solution was evaporated and applied to a column of silica gel for purification (eluting solvent, 1:1 hexanes–ether). There were two fractions. Evaporation of the first fraction gave a white solid (460.2 mg), which was indicated by 1H-NMR spectrum to be a cis,trans-mixture of products 133 (Z:E = 2.55:1). The second fraction was evaporated to afford the pure trans-product 133 (3.346 g). The total trans-product was 3.676 g (93.5%),
the total cis-product 130 mg (3.3%), and the total ratio of trans- and cis-products 97:3. The chromatographically homogeneous trans-product 133 from the second fraction was further recrystallized from 3:1 hexanes–ether to give crystalline needles, mp 60.0–61.5 °C; [α]D +59.2° (c 1.00, CHCl₃); NMR data (1H, 300 MHz, CDCl₃): δ 7.33–7.11 (m, 20H, 4CH₂Ph), 6.96 (dt, 1H, J₂,₃ 15.7 Hz, J₃,₄ =J₃,₄b 7.2 Hz, H-3), 5.91 (d, 1H, H-2), 4.93–4.43 (8d, 8H, 4CH₂Ph), 4.15 (m, 1H, H-1'), 3.77–3.55 (m, 6H, H-2', H-3', H-4', H-5', H-6'a, H-6'b), 3.71 (s, 3H, CO₂CH₃), 2.61 (m, 2H, H-4a, H-4b); (13C, 75 MHz, CDCl₃): δ166.55 (CO₂CH₃), 145.38 (C-3), 138.56, 138.06, 137.94, 128.40, 128.31, 128.26, 127.82, 127.76, 127.66, 127.55, 122.95 (C-2), 82.14, 79.65, 76.56, 75.34, 74.96, 73.45, 73.31, 73.13, 71.51, 68.76, 51.31, 28.45 (C-4); MS: m/z 623 (M + H)+, 622 (M)+, 591(M - OMe)+, 523 (M - CH₂CHCHCO₂CH₃)+.


**Synthesis of Methyl (E)-4-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-but-2-enoate (134).** — To a solution of 2-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)ethanal (131, 2.96 g, 7.93 mmol) in dry benzene (6 mL) was added methyl (triphenylphosphoranylidene)acetate (5.30 g, 15.87 mmol), and the solution was refluxed overnight. TLC showed the complete disappearance of the starting material 131 (Rf 0.25, EtOAc) and a major spot for the product 134 (Rf 0.40, EtOAc). The solution was diluted with dichloromethane (150 mL), washed with brine, dried over Na₂SO₄, concentrated and loaded on a short column of silica gel to remove the unreacted Wittig reagent (eluting solvent, EtOAc). Evaporation of the eluate gave a white solid, which was an inseparable mixture
of the product 134 with triphenylphosphine oxide. The crude white solid product was dissolved in dry methanol (20 mL) and to the solution was added a solution of sodium methoxide in methanol (20%, 0.1 mL). After 15 min, the solution was neutralized with dry ice and evaporated to a yellow solid, which was washed with EtOAc thoroughly to remove triphenylphosphine oxide. A white solid was obtained, which was dried under vacuum overnight and then dissolved in pyridine (50 mL) and acetic anhydride (25 mL). The solution was stirred at room temperature overnight, poured into ice-water, and the product was extracted with dichloromethane (3X100 mL). The combined dichloromethane solution was washed with 3% HCl, sat. NaHCO₃ and brine, dried over Na₂SO₄, and evaporated to a light-yellow syrup, which contained some pyridine salt and was purified on a short column of silica gel (eluting solvent, EtOAc). Evaporation of the eluate afforded a white solid product 134 (2.00 g, 59%). Further recrystallization from 2:1 hexanes-EtOAc gave a colorless needle crystals, mp 136–137 °C; [α]D +69.0° (c 1.52, CHCl₃); NMR data (1H, 300 MHz, CDCl₃): δ 6.89 (dt, 1H, J₂,₃ 15.7 Hz, J₃,₄a =J₃,₄b 7.0 Hz, H-3), 6.02 (d, 1H, JNH,2' 8.4 Hz, N-H), 5.91 (d, 1H, H-2), 5.00 (dd, 1H, J₂,₃ 7.3 Hz, J₃,₄a 6.0 Hz, H-3'), 4.87 (t, 1H, J₄,₅ 6.0 Hz, H-4'), 4.37 (dd, 1H, J₅,₆a 7.5 Hz, J₆a,₆b 12.0 Hz, H-6'a), 4.20 (m, 2H, H-1' and H-2'), 4.06 (dd, 1H, J₅',₆b 3.7 Hz, H-6'b), 3.91 (m, 1H, H-5'), 3.69 (s, 3H, CO₂CH₃), 2.51 (m, 1H, H-4a), 2.37 (m, 1H, H-4b), 2.06, 2.05, 2.03, 1.96 (4s, 4X3H, 4COCH₃); (¹³C, 75 MHz, CDCl₃): δ 170.5, 170.4, 169.6, 168.7 and 166.2 (5CO), 143.6 (C-3), 123.4 (C-2), 71.3 (C-5'), 69.5 (C-1'), 69.4 (C-3'), 67.4 (C-4'), 61.0 (C-6'), 51.3 (CO₂CH₃), 49.9 (C-2'), 30.8 (C-4), 23.0, 20.7, 20.6 and 20.4 (4COCH₃); MS: m/z 430 (M + H)⁺, 398 (M - OMe)⁺, 388 (M + H - CH₂CO)⁺, 370 (M + H - HOAc)⁺, 356 (M + H - HOH - CH₂CO)⁺, 310 (M + H - 2HOAc)⁺.

**Synthesis of methyl (E)-4-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-\alpha-D-glucopyranosyl)-but-2-enoate (135).** — To a solution of 2-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-\alpha-D-glucopyranosyl)ethanal (132, 1.49 g, 3.49 mmol) in dry benzene (13 mL) was added methyl (triphenylphosphoranylidene)acetate (2.34 g, 7.01 mmol). The reaction solution was refluxed for 7 h, whereupon TLC showed the complete disappearance of the starting material 132 (R\textsubscript{f} 0.37, 1:1 hexanes-EtOAc) and a major spot for the sugar ester product 135 (R\textsubscript{f} 0.50, 1:1 hexanes-EtOAc). The solution was cooled to room temperature, diluted with dichloromethane (300 mL), washed with brine, and dried over Na\textsubscript{2}SO\textsubscript{4}. The concentrated solution was charged to a short column of silica gel to remove the unreacted Wittig reagent and triphenylphosphine oxide (eluting solvent, 1:1 hexanes-EtOAc). Evaporation of the effluent gave a light-yellow solid product 135 (1.41 g, 84%), which was recrystallized from 10:3 hexanes-EtOAc to afford a white crystalline product 135, mp 122.5-123.5 °C; [\alpha]_D^\circ +31.1° (c 1.00, CHCl\textsubscript{3}); NMR data (\textsuperscript{1}H, 300 MHz, CDC\textsubscript{3}): δ 7.15 (d, 1H, J\textsubscript{NH,2} 8.9 Hz, N-H), 6.90 (td, 1H, J\textsubscript{2,3} 15.7 Hz, J\textsubscript{3,4a}=J\textsubscript{3,4b} 7.1 Hz, H-3'), 5.95 (d, 1H, H-2), 5.05 (t, 1H, J\textsubscript{2',3'} = J\textsubscript{3',4'} 4.9 Hz, H-3'), 4.87 (dd, 1H, J\textsubscript{4',5} 2.8 Hz, H-4'), 4.60 (ddd, 1H, J\textsubscript{5',6'a} 12.9 Hz, J\textsubscript{5',6'b} 9.6 Hz, H-5'), 4.30 (td, 1H, J\textsubscript{1',2'} = J\textsubscript{1',4'b} 3.4 Hz, J\textsubscript{1',4'a} 9.3 Hz, H-1'), 4.21 (ddd, 1H, H-2'), 4.10 (m, 2H, H-6'a and H-6'b), 3.73 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 2.51 (m, 1H, H-4a), 2.33 (m, 1H, H-4b), 2.14, 2.12 and 2.10 (3s, 3X3H, 3O\textsubscript{2}CC\textsubscript{H}\textsubscript{3}); (\textsuperscript{13}C, 75 MHz, CDC\textsubscript{3}): δ 170.55, 169.42, 168.47, 166.17 (CO\textsubscript{2}CH\textsubscript{3}), 142.78 (C-3), 123.86 (C-2), 72.78, 67.80, 67.43, 66.47, 59.86, 51.39, 49.16, 32.12 (C-4), 20.58, 20.46,
2.040; MS: m/z 484 (M + H)+, 452 (M - OMe)+, 424 (M + H - HOAc)+, 392 (M + H - HOAc - HOMe)+, 364 (M + H - 2HOAc)+.

Anal. Calc for C₁₉H₂₄F₃NO₁₀ (483.389): C, 47.21; H, 5.00; N, 2.90.
Found: C, 47.18; H, 4.99; N, 2.92

**Synthesis of (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-pent-3-en-2-one (136).** — To a solution of 2-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)ethanal (130, 3.20 g, 5.6 mmol) in dry benzene (35 mL) was added 1-triphenylphosphoranylidene-2-propanone (3.59 g, 11.2 mmol), which did not dissolve in the benzene solution completely at room temperature. The suspension was heated at 85 °C and a homogeneous solution was obtained. The solution was refluxed for 18 h and it became red-brown in color. It was impossible to monitor the reaction by TLC because the product 136 and the starting material 130 had the same Rf value (0.41, 1:2 hexanes–ether). The solution was cooled to room temperature, diluted with dichloromethane, washed with brine and dried over MgSO₄. The dried solution was evaporated and the product purified on a column of silica gel (1:2 hexanes–ether). A single fraction was collected and evaporated to a light-yellow solid, which was recrystallized from 4:1 hexanes–ether to afford white crystals of 136 (2.71 g, 79%), mp 104–106 °C; [α]D +57.8° (c 1.12, CHCl₃); NMR data (¹H, 300 MHz, CDCl₃): δ 7.34–7.12 (m, 20H, 4CH₂Ph), 6.77 (dt, 1H, J₄,₅ₐ = J₄,₅₅ 7.1 Hz, J₃,₄ 16.0 Hz, H-4), 6.13 (d, 1H, H-3), 4.95–4.44 (8d, 8H, 4CH₂Ph), 4.17 (m, 1H, H-1'), 3.79–3.60 (m, 6H, H-2', H-3', H-4', H-5', H-6'a and H-6'b), 2.64(m, 2H, H-5a and H-5b), 2.15 (s, 3H, COCH₃); (¹³C, 75 MHz, CDCl₃): δ 198.25 (C-2), 144.19 (C-4), 138.48, 137.96, 137.88, 137.81, 133.16 (C-3), 128.40, 128.30, 128.25, 127.79, 127.74, 127.67, 127.58, 127.55, 82.10,
79.64, 77.84, 75.35, 74.95, 73.42, 73.34, 73.21, 71.48, 68.82, 28.79 (C-5), 26.52 (C-1); MS: m/z 607 (M + H)+, 515 (M - CH2Ph)+, 499 (M - OCH2Ph)+, 407 (M - HOCH2Ph - CH2Ph)+.


**Synthesis of 4(R)-acetonyl-(2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyran)-[3,2-b]-pyrroldine (138).** — To a solution of 2-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)ethanal (131, 1.3450 g, 3.60 mmol) in dry benzene (11 mL) was added 1-triphenylphosphoranylidene-2-propanone (2.2945g, 7.30 mmol). The mixture was refluxed for 24 h to afford a clear brown solution, which was diluted with dichloromethane (300 mL), washed with brine, and dried over Na2SO4. TLC showed the complete disappearance of starting material 131 (RF 0.25, EtOAc) and a major spot was observed for the bicyclo-product 138 (RF 0.42, EtOAc). The solution was concentrated and charged to a column of silica gel for purification (eluting solvent, EtOAc). The major fraction gave 138 as a solid foam product (1.1877 g, 80%). It was very difficult to crystallize this foamy solid product, which had [α]D +124.7° (c 1.05, CHCl3); NMR data (1H, 500 MHz, CDCl3): δ 5.17 (dt, 1H, J2',3' 9.6 Hz, J3',4' 10.0 Hz, H-3'), 4.95 (t, 1H, J4',5' 10.0 Hz, H-4'), 4.52 (m, 1H, H-1'), 4.35 (m, 1H, H-4), 4.27 (dd, 1H, J5',6'a 4.6 Hz, J6'a,6'b 12.3 Hz, H-6'a), 4.06 (dd, 1H, J5',6'b 2.0 Hz, H-6'b), 3.95 (m, 2H, H-2' and H-5'), 3.47 (dd, 1H, J3a,4 3.1 Hz, J3a,3b 17.7 Hz, H-3a), 2.57 (dd, 1H, J3b,4 10.3 Hz, H-3b), 2.51 (m, 1H, H-5a), 2.13 (s, 3H, COCH3), 2.06 (s, 9H, 3COCH3), 2.01 (s, 3H, COCH3), 1.89 (m, 1H, H-5b); (13C, 63 MHz, CDCl3): δ 206.44 (C=O), 170.51, 169.76, and 169.42 (3 O2CCH3, NHCOCH3), 74.03,
73.24, 69.96, 67.87, 62.10, 58.90, 51.69, 49.35, 30.71, 30.11, 22.26, 20.62, 20.47; MS.: m/z 414 (M + H)+, 372 (M + H - CH₂CO)+, 370 (M + H - HCOCH₃)+, 353 (M - HOAc)+.


**Synthesis of (E)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)-pent-3-en-2-one (139) and 4-acetonyl-(3,4,6-tri-O-acetyl-1,2-dideoxy-2-trifluoroacetamido-α-D-glucopyranono)-[3,2-b]-pyrrolidine (140).** — To a solution of 2-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)ethanal (132, 1.48 g, 3.45 mmol) in dry benzene (11 mL) was added 1-triphenylphosphoranylldene-2-propanone (2.22 g, 7.00 mmol). After heating, a clear solution was obtained. The reaction solution was refluxed for 18 h whereupon TLC showed two closely spaced spots for sugar compounds. The reaction solution was cooled to room temperature, diluted with dichloromethane (300 mL), and dried over Na₂SO₄. The concentrated solution was loaded on a column of silica gel, which was eluted with 1:1.5 hexanes–EtOAc. The first fraction (Rf 0.60, 1:1.5 hexanes–EtOAc) was evaporated to give a solid (481.3 mg, 31%), which was identified by its ¹H-NMR spectrum as the bicyclo-product 140. Compound 140 was obtained as a mixture of 4R and 4S diastereoisomers in the ratio of 1.40:1.00; [α]D +58.6° (c 1.39, CHCl₃); MS: m/z 468 (M + H)+, 426 (M + H - CH₂CO)+, 408 (M + H - HOAc)+, 384 (M + H - CH₂CH₂CH₂COCH₃)+, 306 (M + H - 2HOAc - CH₂CO)+. It was found impossible to separate the 4R and 4S diastereoisomers of compound 140.
Anal. Calc for C\textsubscript{19}H\textsubscript{24}F\textsubscript{3}NO\textsubscript{9} (467.390): C, 48.83; H, 5.18; N, 3.00.

Found: C, 48.63; H, 5.21; N, 2.89.

The second fraction (R\textsubscript{f} 0.50, 1:1.5 hexanes-EtOAc) was evaporated to give a white solid product 139 (1.05 g, 67%). Recrystallization of this white solid gave white sand-like crystals, mp 124.5–125.5 °C; [\alpha]\textsubscript{D} +41.5° (c 1.11, CHCl\textsubscript{3}); NMR data (\textsuperscript{1}H, 300 MHz): \delta 7.15 (d, 1H, J\textsubscript{NH,2'} 9.2 Hz, N-H), 6.74 (td, 1H, \textit{J}_3,4 16.0 Hz, H-4), 6.17 (d, 1H, H-3), 5.04 (t, 1H, \textit{J}_2,3' = \textit{J}_3,4' 4.9 Hz, H-3'), 4.88 (dd, 1H, \textit{J}_4',5' 3.0 Hz, H-4'), 4.63 (ddd, 1H, \textit{J}_5',6' 13.1 Hz, \textit{J}_6',5' 9.4 Hz, H-5'), 4.33 (ddd, 1H, \textit{J}_1',2' 3.2 Hz, \textit{J}_1',5a 9.0 Hz, \textit{J}_1',5b 4.5 Hz, H-1'), 4.21 (ddd, 1H, H-2'), 4.08 (m, 2H, H-6'a and H-6'b), 2.51 (ddd, 1H, \textit{J}_5a,5b 15.3 Hz, H-5a), 2.38 (m, 1H, H-5b), 2.26 (s, 3H, COCH\textsubscript{3}), 2.15, 2.12 and 2.09 (3s, 3X3H, 3O\textsubscript{2}CHCH\textsubscript{3}); (\textsuperscript{13}C, 75 MHz, CDCl\textsubscript{3}): \delta 197.65, 170.48, 169.40, 168.40, 156.80, 141.31, 133.52, 73.04, 67.80, 67.52, 66.45, 59.93, 49.21, 32.45, 27.04, 20.60, 20.48; MS: \textit{m/z} 468 (M + H)+, 426 (M + H - CH\textsubscript{2}CO)+, 408 (M - OAc)+, 384 (M - CH\textsubscript{2}CHCHCOCH\textsubscript{3})+.

Anal. Calc for C\textsubscript{19}H\textsubscript{24}F\textsubscript{3}NO\textsubscript{9} (467.390): C, 48.83; H, 5.18; N, 3.00.

Found: C, 48.78; H, 5.21; N, 3.03.

The \textsuperscript{1}H-NMR spectrum of the mother liquor showed the presence of (E)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-\beta-D-glucopyranosyl)-pent-3-en-2-one, whose presence is attributable to the impurity 2-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-\beta-D-glucopyranosyl)ethanal present in the starting material. The pure \beta-product was obtained as needles after chromatography of the mother liquor on a column of silica gel with the eluting solvent 1:1 CHCl\textsubscript{3}-hexanes followed by recrystallization from 2:1 CHCl\textsubscript{3}-hexanes; mp 188.5–189.5 °C; [\alpha]\textsubscript{D} -25.9° (c 0.675, CHCl\textsubscript{3}); NMR data (\textsuperscript{1}H, 300 MHz, CDCl\textsubscript{3}): \delta 7.30 (d, 1H, J\textsubscript{NH,2'} 9.5 Hz, N-H), 6.80 (td, 1H, \textit{J}_{4,5a} = \textit{J}_{4,5b} 6.9 Hz, \textit{J}_{3,4} 16.0 Hz, H-4),...
6.15 (d, 1H, H-3), 5.18 (dd, 1H, J_{2',3'} 9.9 Hz, J_{3',4'} 9.6 Hz, H-3'), 5.08 (t, J_{4',5'} 9.6 Hz, H-4'), 4.24 (dd, 1H, J_{5',6'a} 5.1 Hz, J_{5'a,6'b} 12.3 Hz, H-6'a), 4.11 (dd, 1H, J_{5',6'b} 2.2 Hz, H-6'b), 4.08 (ddd, 1H, J_{1',2'} 11.4 Hz, H-2'), 3.66 (m, 2H, H-5a and H-5b); (^{13}C, 75 MHz, CDCl3): δ 198.32, 171.49, 170.57, 169.17, 141.70, 133.08, 75.81, 73.40, 68.20, 62.10, 54.19, 34.53, 27.19, 20.57, 20.41, 20.28; MS: m/z 468 (M + H)^+, 426 (M + H - CH_2CO)^+, 408 (M + H - HOAc)^+, 384 (M - CH_2CHCHCOCH_3)^+, 366 (M + H - HOAc - CH_2CO)^+, 348 (M + H - 2HOAc)^+, 307 (M - 2OAc - CH_2CO)^+.

**Anal. Calc for C_{19}H_{24}F_3N_0_9 (467.390):** C, 48.83; H, 5.18; N, 3.00. Found: C, 48.81; H, 5.22; N, 3.02.

**Synthesis of (E)-3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-nitro-propene (142).** — To a stirred solution of 2-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)ethanal (130, 3.00 g, 5.3 mmol) in dry methanol (10 mL) and nitromethane (2.9 mL, 54.1 mmol) was added a freshly made solution of sodium methoxide in methanol (Na, 177.0 mg, 7.7 mmol; methanol, 6 mL) under nitrogen. The solution was stirred at room temperature under nitrogen and a white solid precipitate appeared gradually. After 2 h, much white solid precipitated out of solution and then the solution was acidified with acetic acid (0.5 mL). The solvents were removed under vacuum to give a yellow, solid intermediate 141, which was dissolved in dichloromethane (150 mL). The solution was washed with brine, dried over MgSO_4, filtered, and the filtrate was evaporated to a light-yellow solid. Without further purification, the completely vacuum-dried yellow solid intermediate 141 was suspended in acetic anhydride (50 mL) and to the solution was added sodium acetate (3.03 g, 36.9 mmol). The suspension was stirred at room
temperature under nitrogen. After 24 h, an aliquot of solution was taken, washed with sat. NaHCO₃ and extracted with ether. The TLC of the sample showed three spots. The first spot (Rf 0.71, 1:2 hexanes–ether) corresponded to the nitroalkene product 142. The second one (Rf 0.59, 1:2 hexanes–ether) was the intermediate 3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-acetyl-1-nitro-propane, whose spot became lighter and lighter with continuance of the elimination reaction. The third spot (Rf 0.45, 1:2 hexanes–ether) was the intermediate 3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-hydroxy-1-nitro-propane 141, which disappeared completely after 48 h. After 72 h, TLC showed the completion of the reaction. The solution was poured into sat. aqueous NaHCO₃, whereupon a yellow solid product precipitated out, and was separated and dissolved in dichloromethane. The aqueous solution was extracted with dichloromethane (4 X 75 mL). The combined extracts were washed with brine, dried over MgSO₄, filtered and evaporated to give a light-yellow solid, which was recrystallized from methanol (40 mL) to afford a white solid product 142 (2.1 g, 66%). Further recrystallization of the white solid product from 2-propanol gave a white crystalline product 142, mp 108.0–110.5 °C; [α]D +61.4° (c 1.23, CHCl₃); NMR data (¹H, 300 MHz, CDCl₃): δ 7.37–7.12 (m, 20H, 4CH₂Ph), 7.26 (dt, 1H, J₁,₂ 13.5 Hz, J₂,₃a = J₂,₃b 7.2 Hz, H-2), 7.06 (d, 1H, H-1), 4.92–4.45 (8d, 8H, 4CH₂Ph), 4.12 (m, 1H, H-1'), 3.77–3.54 (m, 6H, H-2', H-3', H-4', H-5', H-6'a, H-6'b), 2.65 (m, 2H, H-3a, H-3b); (¹³C, 75 MHz, CDCl₃): δ 140.82 (C-2), 138.74 (C-1), 138.33, 137.87, 137.70, 128.49, 128.34, 128.32, 128.03, 127.88, 127.81, 127.74, 127.65, 81.81, 79.25, 77.54, 75.29, 74.92, 73.61, 73.48, 72.66, 71.86, 68.63, 24.98 (C-3); MS: m/z 610 (M + H)⁺, 608 (M - H)⁺, 518 (M - CH₂Ph)⁺.
Anal. Calc for C\textsubscript{37}H\textsubscript{39}NO\textsubscript{7} (609.714): C, 72.89; H, 6.45; N, 2.30. Found: C, 72.74; H, 6.44; N, 2.30.

**Synthesis of (E)-5-(2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-glucopyranosyl)-2-triisopropylsiloxy-penta-1,3-diene (143).** — To a solution of potassium bis(trimethylsilyl)amide (3.4 mL of 0.5 M solution in toluene) in dry tetrahydrofuran (1 mL) at -22 °C under argon was slowly added a solution of (E)-5-(2,3,4,6-tetra-O-benzyl-\(\alpha\)-D-glucopyranosyl)-pent-3-en-2-one (136, 606.7 mg, 1.0 mmol) in dry THF (1 mL). After addition, the solution was stirred at -22 °C for another 10 min. Then to the solution was added at once the mixture of triisopropylsilyl trifluoromethanesulfonate (0.54 mL, 1.9 mmol) and triethylamine (0.21 mL, 1.5 mmol) in dry THF (1 mL). A white precipitate was soon observed and the solution was stirred at -22 °C for another 30 min. TLC showed the complete disappearance of starting material 136 (\(R_f\) 0.20, 1:1 hexanes–ether) and a single spot for the product 143 (\(R_f\) 0.80, 1:1 hexanes–ether). The solution was warmed to room temperature, diluted with dichloromethane (150 mL), washed with brine, dried over MgSO\textsubscript{4}, filtered, and the filtrate evaporated to give a light-yellow syrup, which still contained some residual salt. The crude syrupy product was dissolved in triethylamine (0.5 mL) and charged to a short column of silica gel to remove the salts (eluting solvent, 3:1 hexanes–ether). Evaporation of the eluate afforded 143 as a colorless syrup (762.5 mg, 99%); NMR data (\(^1\text{H}, 300 \text{ MHz}, \text{C}_6\text{D}_6\): \(\delta\) 7.38–7.04 (m, 20H, 4\text{CH}_2\text{Ph}), 6.38 (dt, 1H, \(J_{3,4} = 15.2 \text{ Hz}, J_{4,5a} = J_{4,5b} = 7.3 \text{ Hz}, J_4 = 7.3 \text{ Hz}, J_3 = 7.3 \text{ Hz}, J_2 = 7.3 \text{ Hz}, J_1 = 7.3 \text{ Hz}, J_0 = 7.3 \text{ Hz}), 6.00 (d, 1H, H-3), 4.98–4.31 (8d, 8H, 4\text{CH}_2\text{Ph}), 4.35 (s, 1H, H-1a), 4.25 (s, 1H, H-1b), 4.15 (m, 1H, H-1'), 3.87–3.65 (m, 6H, H-2, H-3, H-4, H-5, H-6, and H-7), 2.55 (m, 2H, H-5a and H-5b), 1.37–0.88 (m, 21H, Si(C\textsubscript{3}H\textsubscript{7})\textsubscript{3}); (\(^{13}\text{C}, 75 \text{ MHz}, \text{C}_6\text{D}_6\): \(\delta\) 155.80,
Diels-Alder reaction of (E)-3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-nitro-1-propene (142) with (E)-1-methoxy-3-(trimethylsilyl oxy)-1,3-butadiene: — The glassware was base washed and dried at 120 °C oven over night. To a solution of α,β-unsaturated nitroalkene 142 (262.0 mg, 0.43 mmol) in dry toluene (2 mL) was added (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (0.25 mL, 1.16 mmol). The solution was refluxed for 16 h under Ar. TLC showed the complete disappearance of the starting sugar dienophile 142 (RF 0.53, 1:1 hexanes-ether) and a major spot for the cycloaddition intermediates (RF 0.62, 1:1 hexanes-ether). The toluene solvent was removed and the residue was dissolved in THF (3 mL). To the solution was added 0.5 M HCl (1 mL). After 6 h, TLC showed the completion of hydrolysis. The acidic solution was neutralized with sat. NaHCO₃ and the mixture was extracted with dichloromethane. The dichloromethane solution was combined, washed with brine, dried over MgSO₄, filtered, and evaporated to a yellow syrup, which was purified on a silica gel column eluting with 1:3 hexanes-ether). There were two fractions. The first one (RF 0.38, 1:1 hexanes-ether) was the mixture of two exo-addition diastereomers 144 and 145. Before the evaporation of solvents from the first fraction, a white solid (166.0 mg) precipitated out directly and was recrystallized from 5:1 hexanes–EtOAc to provide white crystals of a single exo-diastereoisomer, mp 134–135 °C; [α]D
+22.8° (c 0.77, CHCl₃); NMR data (¹H, 500 MHz, CDCl₃): δ 7.37–7.13 (m, 20H, 4CH₂Ph), 4.88–4.45 (8d, 8H, 4CH₂Ph), 4.66 (1, 1H, J₃,₄ = J₄,₅ 10.5 Hz, H-4), 3.93 (m, 2H, H-4, H-1'), 3.66–3.55 (m, 6H, H-2', H-3', H-4', H-5', H-6'a and H-6'b), 3.34 (s, 3H, OCH₃), 2.92 (ddd, 1H, J₂e,₆e 1.7 Hz, J₂e,₃ 5.0 Hz, J₂e,₂a 14.5 Hz, H-2e), 2.76 (ddd, 1H, J₆e,₅ 4.5 Hz, J₆e,₆a 14.8 Hz, H-6e), 2.44 (m, 1H, H-6), 2.38 (dd, 1H, J₂a,₃ 10.7 Hz, H-2a), 2.19 (dd, 1H, J₆a,₅ 13.6 Hz, H-6a), 1.90 (dd, 1H, J₇R,₇S 15.3 Hz, J₇R,₅ 2.6 Hz, J₇R,₁ 3.8 Hz, H-7R), 1.75 (ddd, 1H, J₇S,₅ 7.3 Hz, J₇S,₁ 10.8 Hz, H-7S); (¹³C, 75 MHz, CDCl₃): δ 203.65 (C-1), 138.41, 137.96, 137.84, 137.77, 128.46, 128.29, 128.15, 128.05, 127.91, 127.80, 127.66, 127.58 (aromatic carbons), 94.09, 92.67, 81.61, 79.34, 78.37, 77.49, 76.82, 75.23, 74.83, 73.44, 73.35, 73.22, 73.15, 71.88, 68.82, 57.30, 43.57, 43.50, 35.68 and 26.62; MS: m/z 710 (M + H)⁺, 678 (M - OMe)⁺, 663 (M - NO₂)⁺, 618 (M - CH₂Ph)⁺.

Anal. Calc for C₄₂H₄₇NO₉ (709.833): C, 71.07; H, 6.67; N, 1.97. Found: C, 70.99; H, 6.69; N, 1.98.

The ¹H-NMR spectrum of the original sample from the first fraction showed that it was a mixture of two diastereomers from exo-addition reaction in the ratio of 1.00:1.13 from integrations of single methoxy peaks at δ 3.33 and 3.31, respectively. The total product from the first fraction was 202.8 mg.

The second fraction was evaporated to a colorless syrup (49.9 mg), which was demonstrated by the ¹H-NMR spectrum to be a mixture of two diastereomers 146 and 147 from endo-addition reaction in the ratio of 1:1.24 from the integration of two single methoxy peaks at δ 3.29 and 3.28, respectively.

The total yield for the cycloaddition reaction was 252.7 mg (83%), including exo-addition products 144 and 145 (202.8 mg, 66.5%) and endo-
addition products 146 and 147 (49.9 mg, 16.4%). The ratio of exo-addition to endo-addition was 80:20. The facial selectivity for exo-addition reaction was 53:47 (integrating methoxy peaks at δ 3.33 and 3.31) and for endo-addition 45:55 (integrating methoxy peaks at δ3.29 and 3.28).

**Diels-Alder reaction of methyl (E)-4-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-but-2-enoate (134) with (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene:** — To a solution of α,β-unsaturated amino sugar ester 134 (257.7 mg, 0.60 mmol) in dry xylene (2 mL) in a reaction vial was added (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (0.30 mL, 1.39 mmol). The reaction solution in the tightly, capped reaction vial was heated for 24 h at 225 °C. TLC showed the complete disappearance of the starting sugar dienophile 134 (Rf 0.46, EtOAc) and a major spot for the cycloaddition intermediates (Rf 0.52, EtOAc). The solution was allowed to cool to room temperature and then 1M Bu₄NF in THF (0.30 mL) was added to the solution to remove the trimethylsilyl protecting group in the cycloaddition intermediates. After 10 min, the reaction solution was diluted with dichloromethane (200 mL), washed with brine, dried over Na₂SO₄, filtered and evaporated to a yellow syrup, which was purified on a column of silica gel, eluting with EtOAc. The first fraction (Rf 0.39, EtOAc) was evaporated to a white solid (43.3 mg), whose ¹H-NMR spectrum indicated it to be a single diastereomer 156 or 157 arising from exo-addition. The white solid was recrystallized from 2:1 hexanes–CHCl₃ to afford colorless long needles, mp 183–184 °C; [α]D +29° (c 0.50, CHCl₃); NMR data (¹H, 300 MHz, CDCl₃): δ 5.99 (d, 1H, JNH₂ 8.8 Hz, N-H), 4.95 (dd, 1H, J₂,₃ 7.2 Hz, J₃,₄ 6.1 Hz, H-3'), 4.87 (dd, 1H, J₄,₅ 5.7 Hz, H-4'), 4.33 (dd, 1H, J₆a,₆b 12.1 Hz, J₅,₆a 7.4 Hz, H-6'a),
4.15 (m, 3H, H-2', H-1' and H-6'b), 3.90 (ddd, 1H, J_2^1,6^2 3.4 Hz, H-5'), 3.77 (s, 3H, CO_2CH_3), 3.73 (ddd, J_2a,3 3.4 Hz, J_2a,3 9.5 Hz, J_3,4 8.2 Hz, H-3), 3.30 (s, 3H, OCH_3), 2.84 (dd, 1H, J_2a,2e 14.2 Hz, H-2e), 2.67 (m, 2H, J_4,5 8.5 Hz, H-6e and H-4), 2.36 (dd, 1H, H-2a), 2.01 (m, 2H, H-6a and H-5), 2.11, 2.09, 2.08 and 1.99 (4s, 4X3H, 4COCH_3), 1.60 (m, 2H, H-7a and H-7b); (^{13}C, 63 MHz, CDCl_3): δ 206.32 (C-1), 173.64, 170.71, 170.33, 169.60 and 168.80 (3O_2CCH_3, NHCOCH_3, CO_2CH_3), 78.96 (C-3), 71.63 (C-5'), 69.59 (C-1'), 69.20 (C-3'), 67.37 (C-4'), 61.16 (C-6'), 56.85 (OCH_3), 53.51 (C-4), 52.17 (CO_2CH_3), 49.86 (C-2'), 45.80 (C-6), 44.65 (C-2), 33.76 (C-5), 32.57 (C-7), 23.05 (NHCOCH_3), 20.77, 20.72 and 20.65 (3O_2CCH_3); MS: m/z 530 (M + H)^+, 498 (M - OMe)^+, 488 (M + H - CH_2CO)^+, 470 (M - OAc)^+.

Anal. Calc for C_{24}H_{35}NO_{12} • 0.25CHCl_3 (559.380): C, 52.07; H, 6.35; N, 2.50. Found: C, 52.06; H, 6.37; N, 2.54.

The second fraction (R_f 0.35, EtOAc) was evaporated to a syrup (149.7 mg), which was demonstrated by its ^1H-NMR spectrum to be a mixture of two diastereomers 156 and 157 from exo-addition, with the chemical shifts of methoxy peaks at δ 3.32 and 3.30, respectively, plus one diastereomer 158 or 159 from the endo-addition with a methoxy peak at δ 3.26 and N-H peak at δ 6.46. The integrations of methoxy peaks at δ 3.32, 3.30, and 3.26 showed the ratio of the three diastereoisomers to be 3.05:1.03:1.00.

The third fraction (R_f 0.20, EtOAc) was evaporated to a syrup (39.5 mg), whose ^1H-NMR spectrum showed that it was a mixture of one diastereoisomer from exo-addition (with the chemical shift of the methoxy peak at δ 3.32) and one from the endo-addition mode and having the methoxy peak at δ 3.26 and N-H peak at δ 5.89. The integrations of methoxy peaks indicated the ratio of the two diastereomers to be 1:6.66.
As a summary, the total yield for the cycloaddition reaction was 232.5 mg (73.2%), and the ratio of exo-addition to endo-addition was 73:27. The facial selectivity in exo-addition was 56:44 and in endo-addition 54:46.

When the cycloaddition reaction intermediates was worked up with 3% HCl, not only was the trimethylsilyl protecting group removed, but also the elimination of HOMe from the central cyclohexanone ring occurred for the endo-adducts. The elimination products showed the same Rf value in TLC as the first separated exo-addition diastereoisomer 156 or 157 (Rf 0.39, EtOAc). After purification on a column of silica gel (eluting solvent, EtOAc), the last fraction (Rf 0.35, EtOAc) was evaporated to a white solid, which was recrystallized from 1:1 hexanes–EtOAc to give colorless needle crystals, mp 194–195 °C; [α]D +54.3° (c 0.56, CHCl₃). NMR spectra showed that it was another exo-addition product 157 or 156. NMR data (¹H, 300 MHz, CDCl₃): δ 5.86 (d, 1H, J₉₂,₃ 7.9 Hz, N-H), 4.95 (dd, 1H, J₂₃,₄ 7.4 Hz, J₃,₄ 6.9 Hz, H-3'), 4.89 (dd, 1H, J₄,₅ 6.6 Hz, H-4'), 4.28 (dd, 1H, J₅₆,₆ 12.1 Hz, J₅,₆ 6.9 Hz, H-6'a), 4.21 (m, 2H, H-2', H-1'), 4.14 (dd, 1H, J₅,₆ 3.4 Hz, H-6'b), 3.81 (m, 1H, H-5'), 3.80 (s, 3H, CO₂CH₃), 3.68 (ddd, 1H, J₂a,₃ 4.4 Hz, J₂a,₃ 10.4 Hz, J₃,₄ 9.1 Hz, H-3), 3.32 (s, 3H, OCH₃), 2.89 (ddd, 1H, J₂a,₆ 1.3 Hz, J₂a,₂a 14.0 Hz, H-2a), 2.63 (dd, 1H, J₄,₅ 10.5 Hz, H-4), 2.57 (dd, 1H, J₆a,₆ 13.3 Hz, H-6a), 2.35 (dd, 1H, H-2a), 2.17 (m, 2H, H-6a and H-5), 2.09, 2.08, 2.07 and 1.97 (4s, 4X3H, 4COCH₃), 1.76 (m, 1H, H-7a), 1.33 (m, 1H, H-7b); (¹³C, 75 MHz, CDCl₃): δ 205.59 (C-1), 173.57, 170.76, 170.49, 169.50, 168.76 (3O₂CCCH₃, NHCOCH₃, CO₂CH₃), 78.65, 70.65, 69.75, 67.57, 67.28, 61.22, 56.75, 54.20, 51.98, 50.49, 45.03, 43.65, 31.31, 30.93, 23.00 (NHCOCH₃), 20.67, 20.61 and 20.55 (3O₂CCCH₃); MS: m/z 530 (M + H)⁺, 498 (M - OMe)⁺, 488 (M + H - CH₂CO)⁺, 470 (M - OAc)⁺.

Diels-Alder reaction of methyl (E)-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-but-2-enoate (133) with (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene: — To a solution of α-C-glycosyl dienophile 133 (355.5 mg, 0.57 mmol) in dry xylene (2 mL) in a conical reaction vial was added (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (0.30 mL, 1.39 mmol). The reaction vial was capped tightly and heated at 210–215 °C for 24 h. TLC showed the complete disappearance of starting sugar dienophile 133 (Rf 0.40, 1:1 hexanes–ether) and one major spot for cycloaddition intermediates (Rf 0.55, 1:1 hexanes–ether). The reaction solution was cooled to room temperature and to the solution was added 1M Bu₄NF in THF (0.5 mL). After 10 min, the red-brown solution was diluted with dichloromethane (200 mL), washed with brine, dried over MgSO₄, filtered and evaporated to a yellow syrup, which was purified on a column of silica gel (eluting with 1:2 hexanes–ether). There were three fractions. The first fraction (Rf 0.38, 1:2 hexanes–ether) was evaporated to a syrup (193.2 mg), whose ¹H-NMR spectrum indicated it to be a mixture of two diastereomers from the exo-addition reaction. The ratio of the two exo-diastereoisomers with methoxy peaks at δ 3.29 and δ 3.28 was determined by integrations of the two methoxy peaks to be 1.00:1.30.

Evaporation of the second fraction gave a syrup (59.8 mg), whose ¹H-NMR spectrum showed it to be a mixture of four diastereomers from the cycloaddition reaction, with methoxy peaks at δ 3.29, 3.28, 3.27, and 3.25,
respectively. Integrations of the four methoxy peaks indicated the ratio to be 3.54:1.10:1.00:1.37.

The third fraction (RF 0.29, 1:2 hexanes–ether) was evaporated to a syrup (71.1 mg). 1H-NMR showed it was a mixture of two diastereomers from the endo-addition reaction, with methoxy peaks at δ 3.27 and 3.25, respectively. The ratio of the two diastereoisomers was determined to be 1.02:1.00 by integrations of the two methoxy peaks.

The total yield of the cycloaddition reaction was 323.8 mg (82%), which included one exo-diasteromer with a methoxy peak at δ 3.29 (114.2 mg), another exo-diastereomer with a methoxy peak at δ 3.28 (118.6 mg), the endo-diastereomer with a methoxy peak at δ3.27 (44.1 mg) and another endo-diastereomer with a methoxy peak at δ 3.25 (46.9 mg). The total exo-addition products weighed 232.8 mg and the endo-addition products 91.0 mg. The ratio of exo-addition to endo-addition was 72:28. The facial selectivity in exo-addition was 49:51 (methoxy peak at δ 3.29 : δ 3.28). The facial selectivity in endo-addition was 48:52 (methoxy peak at δ 3.27 : δ 3.25). MS of the mixture of four diastereomers: m/z 723 (M + H)+, 691 (M - OMe)+, 659 (M - HOMe - Me)+, 631 (M - CH$_2$Ph)+, 615 (M - OCH$_2$Ph)+, 583 (M - HOMe - OCH$_2$Ph)+, 567 (M - 2HOMe - CH$_2$Ph)+, 551 (M - 2HOMe - OCH$_2$Ph)+.

Diels-Alder reaction of methyl (E)-4-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl)-but-2-enoate (135) with (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene: — To a solution of sugar dienophile 135 (193.4 mg, 0.40 mmol) in dry xylene (2 mL) in a reaction vial was added (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (0.50 mL, 2.31 mmol). The solution was heated for 24 h at 200 °C and then
cooled to room temperature. To the solution was added 1 M Bu₄NF in THF (0.5 mL). The solution became red-brown immediately and was stirred at room temperature for 10 min, and then diluted with dichloromethane (200 mL), washed with brine and dried over Na₂SO₄. TLC showed the complete disappearance of sugar dienophile (Rf 0.48, 1:1 hexanes–EtOAc) and a long trailing spot for final cycloaddition products (Rf 0.23, 1:1 hexanes–EtOAc). The solution was evaporated to a syrup, which was purified on a column of silica gel, eluting with 1:1 hexanes–EtOAc. Evaporation of the first fraction gave a light yellow syrup (128.4 mg), which was identified by its ¹H-NMR spectrum to be a mixture of three diastereoisomers, two from exo-addition with chemical shifts of the methoxy peak at δ 3.32 and 3.30, respectively, and one from endo-addition reaction with methoxy peak at δ 3.25. Integrations of the three methoxy peaks indicated the ratio to be 8.28:6.12:1.00 (δ 3.32 : δ 3.30 : δ 3.25). The second fraction was evaporated to a syrup (6.7 mg), which was indicated to be a mixture of four diastereoisomers from the cycloaddition reaction with a ratio of 3.39:10.86:5.94:1.00, as determined by integrations of methoxy peaks at δ 3.32, 3.30, 3.26 and 3.25, respectively. The third fraction was evaporated to syrup (55.3 mg), which was shown by its ¹H-NMR spectrum to be a mixture of three diastereomers, one from exo-addition reaction with a methoxy peak at δ 3.30 and two from endo-addition reaction with methoxy peaks at δ 3.26 and 3.25, respectively. Integrations of the three methoxy peaks indicated the ratio of the three diastereomers to be 1.05:1.28:1.00.

In summary, the total yield of the cycloaddition reaction was 190.4 mg (82%), including exo-addition products (142 mg) and endo-addition products (48.4 mg). The ratio of exo-addition to endo-addition was 75:25. The facial
selectivity in the \textit{exo}-addition reaction was 51:49 and in the \textit{endo}-addition 52:48.

The MS of the mixture of four diastereoisomers showed: \( m/z \) 606 (\( M + Na \))^+, 584 (\( M + H \))^+, 552 (\( M - OMe \))^+, 523 (\( M - HOAc \))^+, 520 (\( M - HOMe - OMe \))^+, 510 (\( M - CH_2CO - OMe \))^+, 478 (\( M - CH_2CO - HOMe - OMe \))^+, 418 (\( M - CH_2CO - HOAc - HOMe - OMe \))^+.

**Diels-Alder reaction of (\( E \))-5-(2,3,4,6-tetra-\( O \)-benzyl-\( \alpha \)-\( \alpha \)-
\( \text{glucopyranosyl} \))-pent-3-en-2-one (136) with (\( E \))-1-methoxy-3-
(\( \text{trimethylsilyloxy} \))-1,3-butadiene: — To a solution of the \( \alpha,\beta \)-unsaturated
methyl ketone 136 (121.4 mg, 0.20 mmol) in dry xylene (1 mL) in a conical
reaction vial was added (\( E \))-1-methoxy-3-(\( \text{trimethylsilyloxy} \))-1,3-butadiene (0.13
mL, 0.60 mmol). The tightly capped reaction vial was heated for 24 h at 210–
215°C. TLC showed the complete disappearance of the starting sugar
dienophile 136 (\( R_f \) 0.38, 1:2 hexanes–ether) and a single spot for the
cycloaddition intermediates (\( R_f \) 0.62, 1:2 hexanes–ether). The solution was
cooled to room temperature, and then to the solution was added 1 M \( Bu_4NF \) in
THF (1 mL). The solution immediately became red-brown in color and was
stirred for 10 min to complete the hydrolysis. The solution was
diluted with dichloromethane (200 mL), washed with brine, dried over MgSO\(_4\),
filtered and evaporated to a red-brown syrup, which was purified on a column of silica gel
eluted with 1:2 hexanes–ether. There were two fractions. The first fraction (\( R_f \)
0.26, 1:2 hexanes–ether) was evaporated to a syrup (79.8 mg), which was
determined by its \( ^1\text{H-NMR} \) spectrum to be a mixture of two diastereomers from
the \textit{exo}-addition mode. The ratio of the two \textit{exo}-diastereoisomers was
determined by integrations of the two single methyl ketone peaks at \( \delta \) 2.25 and
Evaporation of the second fraction (Rf 0.11, 1:2 hexanes–ether) gave a syrup (28.2 mg), which was demonstrated by its $^1$H-NMR spectrum to be a mixture of two diastereomers from the endo-addition reaction. Integrations of the two single methyl ketone peaks at $\delta$ 2.19 and 2.16 showed the ratio of the two endo-diastereomers to be 2.08:1.00. The total yield of the cycloaddition reaction was 108.0 mg (80%) and the ratio of exo-addition to endo-addition was 79:21. The facial selectivity in exo-addition was 48:52 and the facial selectivity in endo-addition was 32:68. MS of the mixture of cycloaddition products: m/z 707 (M + H)$^+$, 675 (M - OMe)$^+$, 567 (M - HOCH$_2$Ph - OMe)$^+$.

**Diels-Alder reaction of (E)-5-(3,4,6-tri-O-acetyl-2-deoxy-2-trifluroacetamido-α-D-glucopyranosyl)-pent-3-en-2-one (139) with (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene:** — To a solution of sugar dienophile 139 (182.9 mg, 0.40 mmol) in dry xylene (1.5 mL) in a reaction vial was added (E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (0.30 mL, 1.39 mmol). The reaction solution was heated for 24 h at 190–195 °C. TLC showed the complete disappearance of starting sugar dienophile 139 (Rf 0.21, 1:1 hexanes–EtOAc) and a major spot for the cycloaddition intermediates (Rf 0.38, 1:1 hexanes–EtOAc). The solution was cooled to room temperature and 1 M Bu$_4$NF in THF (0.5 mL) was added. After 15 min, the solution was diluted with dichloromethane (200 mL), washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated to a yellow syrup, which was purified on a column of silica gel eluted with 1:2 hexanes–EtOAc. There were two fractions. The first fraction (Rf 0.20, 1:1.5 hexanes–EtOAc) contained two exo-addition products (118.5 mg) with chemical shifts of the methoxy peak and the methyl ketone peak at $\delta$ 3.27,
2.29 and δ 3.26, 2.28, respectively. Integrations of the methoxy peaks showed the ratio of two exo-addition products to be 1.44:1.00. Evaporation of the second fraction (Rf 0.08, 1:1.5 hexanes–EtOAc) gave a syrup (36.5 mg), which was demonstrated from its 1H-NMR spectrum to be a mixture of two diastereomers from endo-addition reaction, with the chemical shifts of methoxy peak and methyl ketone peak at δ 3.27, 2.28 and δ 3.26, 2.27, respectively. Integrations of the two methoxy peaks indicated the ratio of two endo-adducts 1.94:1.00.

In summary, the total yield for the cycloaddition reaction was 155 mg (74%). The ratio of exo-addition to endo-addition was 77:23. The facial selectivity in exo-addition was 59:41 and in endo-addition 66:34.

MS of the mixture of four diastereoisomers: m/z 568 (M + H)+, 536 (M - OMe)+, 508 (M - OAc)+, 494 (M - OMe - CH₂CO)+, 476 (M - HOAc - OMe)+, 452 (M - 2CH₂CO - OMe)+.

Diels-Alder reaction of methyl (E)-4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-but-2-enoate (133) with (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-(trisopropylsilyloxy)-penta-1,3-diene (143): — To a solution of sugar diene 143 (240.4 mg, 0.32 mmol) in dry xylene (2 mL) in a reaction vial was added sugar dienophile 133 (313.4 mg, 0.50 mmol). The tightly capped reaction vial was heated for 96 h at 250 °C and then cooled to room temperature. To the solution was added 1 M Bu₄NF in THF (0.5 mL), and the solution was stirred at room temperature for 1 h, diluted with dichloromethane (200 mL), washed with brine, dried over MgSO₄. Evaporation of the solvent gave a yellow syrup, which was purified on a column of silica gel, eluting with 1:1 and 1:2 hexanes–ether. A colorless solid product was obtained
(130.2 mg, 33.6%), which was recrystallized from 4:1 hexanes–EtOAc to afford a white crystalline product 160, mp 101–102 °C; [α]D +36.7° (c 0.845, CHCl3); NMR data (1H, 500 MHz, C6D6): δ 7.38–7.05 (m, 40H, 8CH2Ph), 4.96–4.31 (m, 16H, 8CH2Ph), 4.14 (ddd, 1H, J1",2" 5.9 Hz, J1","S 12.1 Hz, J1","R 2.6 Hz, H-
1"), 3.93 (m, 1H, H-1'), 3.86 (t, 1H, J2",3" = J3",4" 8.6 Hz, H-3"), 3.77–3.64 (m, 10H, H-2', H-3", H-4', H-4", H-5', H-5", H-6'a, H-6''a, H-6'b and H-6''b), 3.58 (dd, 1H, J1",2" 5.9 Hz, J2',3' 9.2 Hz, H-2'), 3.33 (s, 3H, CO2CH3), 3.00 (dd, 1H, J6a,6a 14.4 Hz, J6a,5 2.8 Hz, H-6e), 2.69 (dd, 1H, J2e,2a 14.0 Hz, J2e,3 2.9 Hz, H-
2e), 2.46 (m, 1H, H-3), 2.21 (t, 1H, J3,4 = J4,5 10.9 Hz, H-4), 2.14 (m, 1H, H-5), 2.02 (dt, 1H, J7R,7S 12.1 Hz, J7S,3 -2 Hz, H-7'S), 1.85 (dt, 1H, J7R,7S 14.9 Hz, J7R,5 = J7R,1' -2 Hz, H-7R), 1.80 (dd, 1H, J6a,5 12.7 Hz, H-6a), 1.79 (dd, 1H, J2a,3 13.0 Hz, H-2a), 1.55 (m, 2H, 7S and H-7'R); (13C, 75 MHz, CDCl3): δ 208.17 (C-1), 174.48 (CO2CH3), 138.60, 138.06, 137.98, 128.39, 128.28, 127.84, 127.79, 127.71 and 127.52 (aromatic carbons), 82.28, 81.90, 79.73, 79.57, 79.53, 77.80, 73.97, 72.89, 71.64, 71.16, 70.05, 68.71, 54.69, 51.69, 45.77, 43.97, 39.33, 35.16, 28.96 and 28.62; MS: m/z 1229 (M + H)+, 1197 (M - OMe)+, 1168 (M - HCO2Me)+.


Diels-Alder reaction of (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-pent-3-en-2-one (136) with (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-(triisopropylsilyloxy)-penta-1,3-diene (143):
A. Thermal conditions. — To a solution of the sugar diene 143 (128.0 mg, 0.17 mmol) in dry xylene (2 mL)) in a reaction vial was added the sugar dienophile 136 (101.1 mg, 0.17 mmol). The reaction vial was capped tightly and heated for 96 h at 240–245 °C. The xylene solvent was removed under vacuum and the residue was dissolved in acetone (10 mL). To the solution was added 3% HCl (1 mL) and the solution was stirred at room temperature overnight. Acetone was removed and the residue was dissolved in dichloromethane (150 mL). The solution was washed with sat. NaHCO₃ and brine, dried over Na₂SO₄, filtered and evaporated to a light yellow syrup, which was purified on a column of silica gel, eluting with 1:1 hexanes–ether and 1:2 hexanes–ether. There were two fractions. The first fraction (Rf 0.20, 1:1 hexanes–ether) was evaporated to give unreacted (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-pent-3-en-2-one (136, 56.8 mg). The second fraction (Rf 0.10, 1:1 hexanes–ether) was evaporated to afford a white solid product (70.0 mg, 48%, based on the recovered sugar dienophile), which was demonstrated by its ¹H-NMR spectrum to be a single diastereomer from the exo-addition mode. No endo-addition products could be detected. The white solid product was recrystallized from 4:1 hexanes–ether to provide a white crystalline product 161, mp 140.5–141.5 °C; [α]D +34.7° (c 0.89, CHCl₃); NMR data (¹H, 500 MHz, CDCl₃): δ 7.39–7.12 (m, 40H, 8CH₂Ph), 4.91–4.42 (m, 16H, 8CH₂Ph), 4.01 (ddd, 1H, J₁",₂" 5.9 Hz, J₁",₇R 2.0 Hz, J₁",₇S 11.9 Hz, H-1"), 3.96 (m, 1H, H-1'), 3.72–3.38 (m, 12H, H-2', H-2", H-3', H-3", H-4', H-4", H-5', H-5", H-6'a, H-6"a, H-6'b and H-6"b), 2.75 (dd, 1H, J₆a₆e 14.0 Hz, J₆e₅ 2.9 Hz, H-6e), 2.56 (dd, 1H, J₂₂a 14.7 Hz, J₂₂₃ 4.0 Hz, H-2e), 2.35 (t, 1H, J₃₄ = J₄₅ 10.2 Hz, H-4), 2.23 (m, 1H, H-3), 2.09 (m, 1H, H-5), 2.06 (s, 3H, COCH₃), 2.03 (dd, 1H, J₆₉₅ 12.0 Hz, H-6a), 1.90 (dd, 1H, J₂₃₃ 12.2 Hz, H-2a), 1.72 (m, 2H, H-7R
and H-7'S), 1.55 (m, 1H, 7S), 1.43 (ddd, 1H, J\textsubscript{7'R,7'S} 14.5 Hz, J\textsubscript{7'R,3} 10.5 Hz, H-7'R); (\textsuperscript{13}C, 75 MHz, CDCl\textsubscript{3}): 82.11, 80.89, 80.87, 138.53, 138.42, 138.30, 128.40, 128.30, 128.08, 128.06, 127.92, 127.81, 127.73, 127.68 and 127.58 (aromatic carbons), 82.19, 81.88, 79.54, 77.80, 77.62, 75.40, 75.27, 75.00, 74.89, 73.47, 73.41, 73.23, 71.67, 71.40, 70.20, 68.71, 68.64, 61.51, 45.57, 43.73, 37.90, 34.39, 29.58, 29.54, 29.14 and 28.95; MS: m/z 1214 (M + 2H\textsuperscript{+}), 1198 (M + H - CH\textsubscript{2}Ph\textsuperscript{+}), 1122 (M + H - CH\textsubscript{2}Ph\textsuperscript{+}), 1106 (M - OCH\textsubscript{2}Ph\textsuperscript{+}), 1014 (M + H - CH\textsubscript{2}Ph - HOCH\textsubscript{2}Ph\textsuperscript{+}), 998 (M - 2OCH\textsubscript{2}Ph\textsuperscript{+}).

Anal. Calc for C\textsubscript{78}H\textsubscript{84}O\textsubscript{12} (1213.510): C, 77.20; H, 6.98. Found: C, 77.11; H, 7.01.

B. BF\textsubscript{3}•OEt\textsubscript{2}-catalyzed conditions. — To a stirred solution of the sugar diene 143 (212.1 mg, 0.28 mmol) and sugar dienophile 136 (151.5 mg, 0.25 mmol) in dry toluene (3 mL) was added BF\textsubscript{3}•OEt\textsubscript{2} (0.061 mL, 0.50 mmol) under N\textsubscript{2} at room temperature. The reaction solution was stirred at room temperature for 5 h, and then 1 N HCl (1 mL) was added. The mixture was extracted with dichloromethane and the combined extracts were washed with sat. NaHCO\textsubscript{3}, and dried over MgSO\textsubscript{4}. TLC showed that there were a large amount of sugar dienophile 136 still present in the system (R\textsubscript{F} 0.40, 1:2 hexanes–ether) and one spot for the cycloaddition product (R\textsubscript{F} 0.28, 1:2 hexanes–ether). Evaporation of the solvent gave a syrup, which was charged to a column of silica gel and eluted with 1:2 hexanes–ether. The first fraction provided the sugar dienophile 136 (134.5 mg). The second fraction was evaporated to a solid, which was recrystallized from 2:1 hexanes–ether to afford a crystalline product (16 mg, 9.5%, based on the recovered sugar dienophile),
mp 141-142°C; [α]D +34° (c 0.46, CHCl₃). The ¹H- and ¹³C-NMR spectra showed that it was compound 161.

**C. SnCl₄-catalyzed conditions.** — To a stirred solution of the sugar diene 143 (237.5 mg, 0.31 mmol) and the sugar dienophile 136 (188.6 mg, 0.31 mmol) in dry toluene (1 mL) was added 1 M SnCl₄ in CH₂Cl₂ (0.31 mL, 0.31 mmol) at room temperature under Ar. The reaction solution became dark purple immediately and was stirred at room temperature under Ar for 6 h, then was worked up with 1% HCl (10 mL). The mixture was extracted with dichloromethane and the combined extracts were washed with sat. NaHCO₃ and brine, dried over MgSO₄. The solvent was evaporated and the residue was loaded on a column of silica gel, eluting with 1:2 hexanes–ether. The first fraction (Rf 0.40, 1:2 hexanes–ether) gave the sugar dienophile 136 (26.3 mg). The second fraction (Rf 0.28, 1:2 hexanes–ether) was evaporated to a light yellow solid (170.5 mg, 48%), which was not the cycloaddition products and could not be identified.

**D. TiCl₄-catalyzed conditions.** — To a stirred solution of the sugar diene 143 (140.1 mg, 0.184 mmol) and the sugar dienophile 136 (111.3 mg, 0.184 mmol) in dry toluene (1 mL) was added TiCl₄ (0.02 mL, 0.184 mmol) at room temperature under Ar. A brown solid was formed immediately. The mixture was stirred at room temperature under Ar for 1.5 h, then was worked up with 1% HCl (5 mL). The solution was extracted with dichloromethane and the combined extracts were washed with sat. NaHCO₃ and brine, dried over MgSO₄. TLC showed one major spot (Rf 0.58, 1:2 hexanes–ether) and a very light spot for sugar dienophile 136 (Rf 0.40, 1:2 hexanes–ether). The solvent
was evaporated and the residue was charged to a column of silica gel, eluting with 1:1.5 hexanes–ether. It appeared that the new product reverted to the sugar dienophile 136 again during the purification on a column of silica gel. Only 10.5 mg of new product was obtained, and it was demonstrated to be a single diastereomer 5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-4-chloro-2-pentanone, mp 107–108 °C; ¹H-NMR atα (500 MHz, CDCl₃): δ 7.35–7.13 (m, 20H, 4CH₂Ph), 4.91–4.48 (8d, 8H, 4CH₂Ph), 4.47 (m, 1H, H-4), 4.42 (ddd, 1H, J₃',₂' 6.0 Hz, J₁',₅ₕ 11.6 Hz, J₁',₅ₖ 2.3 Hz, H-1'), 3.78–3.60 (m, 6H, H-2', H-3', H-4', H-5', H-6'a and H-6'b), 3.01 (dd, J₃ₕ,₄ 6.7 Hz, J₃ₕ,₃ₜ 17.4 Hz, H-3a), 2.88 (dd, 1H, J₃ₜ,₄ 7.0 Hz, H-3b), 2.21 (ddd, 1H, J₄ₕ,₅ₕ 2.7 Hz, J₅ₕ,₅ₖ 15.3 Hz, H-5a), 2.13 (s, 3H, COCH₃), 1.94 (ddd, 1H, J₄ₕ,₅ₕ 10.8 Hz, H-5b); MS: m/z 643 (M + H)⁺, 607 (M - Cl)⁺, 551 (M - CH₂Ph)⁺, 535 (M - OCH₂Ph)⁺, 499 (M - HCl - OCH₂Ph)⁺.

The Diels-Alder reaction of (E)-3-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-nitro-propene (142) with (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-(trilsopropylsilyloxy)-penta-1,3-diene (143): — To a solution of the sugar diene 143 (101.5 mg, 0.13 mmol) in dry xylene (2.5 mL) in a reaction vial was added the α,β-unsaturated nitroalkene 142 (128.0 mg, 0.21 mmol). The reaction vial was capped tightly and heated for 24 h at 210–215 °C. The xylene solvent was removed and the residue was dissolved in acetone (5 mL). To the solution was added 3% HCl (1 mL) and the solution was stirred at room temperature overnight. The reaction solution was diluted with dichloromethane (150 mL), washed with sat. NaHCO₃ and brine, dried over Na₂SO₄, and evaporated to a yellow syrup, which was purified on a column of silica gel, eluting with 1:1 hexanes–ether. There were four fractions. The first fraction (Rf 0.48, 1:1.2 hexanes–ether) was evaporated to give the
unreacted sugar dienophile 142 (17.9 mg). The second fraction (Rf 0.43, 1:1.2 hexanes–ether) gave the unidentified compounds (36.5 mg). The third fraction (Rf 0.23, 1:1.2 hexanes–ether) produced (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-pent-3-en-2-one (136,18.6 mg), which resulted from the hydrolysis of unreacted sugar diene 143. Evaporation of the fourth fraction (Rf 0.13, 1:1.2 hexanes–ether) provided a colorless solid product (68.0 mg, 41%, based on the recovered sugar dienophile), which was demonstrated by 1H-NMR to be a single diastereomer 155 from the exo-addition mode. No endo-adducts were detected. The colorless solid product was recrystallized from 3:1 hexanes–toluene to give a white crystalline product 155, mp 148–149 °C; [α]D +340 (c 0.28, CHCl₃); NMR data (1H, 500 MHz, C₆D₆): δ 7.37–7.05 (m, 40H, 8CH₂Ph), 4.93–4.29 (m, 16H, 8CH₂Ph), 4.11 (t, 1H, J₃,₄ = J₄,₅ 10.9 Hz, H-4), 4.06 (ddd, 1H, J₁,₂ = 6.0 Hz, J₁,₇S 12.2 Hz, J₁,₇R 2.5 Hz, H-1"), 3.82 (ddd, 1H, J₁,₂ = 6.0 Hz, J₁,₇S 9.3 Hz, J₁,₇R ~2 Hz, H-1"), 3.78–3.52 (m, 12H, H-2', H-2", H-3', H-3", H-4', H-4", H-5', H-5", H-6'a, H-6"a, H-6'b and H-6"b), 2.90 (dd, 1H, J₆₈,₆₉ 15.2 Hz, J₆₈,₅ 3.2 Hz, H-6e), 2.67 (m, 1H, H-3), 2.62 (dd, 1H, J₂₈,₂₉ 15.9 Hz, J₂₈,₃ 3.0 Hz, H-2e), 2.30 (m, 1H, H-5), 1.97 (ddd, 1H, J₇₈,₇S 14.7 Hz, J₇₈,₃ ~2 Hz, H-7S), 1.83 (ddd, 1H, J₇₈,₇S 15.0 Hz, J₇₈,₅ ~2 Hz, H-7R), 1.76 (dd, 1H, J₆₈,₅ 11.9 Hz, H-6a), 1.73 (dd, 1H, J₂₈,₂₉ 11.8 Hz, H-2a), 1.55 (ddd, 1H, J₇₈,₃ 12.5 Hz, H-7'R), 1.46 (ddd, 1H, J₁,₇S 9.3 Hz, J₅,₇S 9.7 Hz and J₇₈,₇S 15.0 Hz, H-7S); (13C, 75 MHz, C₆D₆): δ 207.14 (C-1), 139.61, 139.50, 139.14, 139.07, 139.02, 138.95, 138.78 and 138.46, 128.74, 128.69, 128.64, 128.51, 128.32, 128.00, 127.77 and 127.68 (aromatic carbons), 93.97 (C-4), 82.83, 82.28, 80.27 (2carbons), 78.78, 78.62, 75.33 (CH₂Ph), 75.20 (CH₂Ph), 75.05 (2CH₂Ph), 74.02 (C-1"), 73.71 (CH₂Ph), 73.66 (CH₂Ph), 73.41 (CH₂Ph), 73.24 (CH₂Ph), 72.59, 72.22, 70.21, 69.97, 69.89 (C-1"), 44.28 (C-6), 42.63 (C-2), 40.58 (C-5),
36.91 (C-3), 27.54 (C-7) and 26.93 (C-7); MS: m/z 1217 (M + 2H)+, 1215 (M)+, 1170 (M + H - NO₂)+, 1125 (M + H - CH₂Ph)+, 1080 (M + H - NO₂ - CH₂Ph)+.

Anal. Calc for C₇₆H₈₁NO₁₃ (1216.470): C, 75.04; H, 6.71; N, 1.15.
Found: C, 74.90; H, 6.69; N, 1.09.

Diels-Alder reaction of methyl (E)-4-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl)-but-2-enoate (134) with (E)-5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2-(trisopropylsilyloxy)-penta-1,3-diene (143): — To a solution of sugar diene 143 (384.0 mg, 0.50 mmol) in dry xylene (2 mL) in a reaction vial was added sugar dienophile 134 (216.1 mg, 0.50 mmol). The tightly capped reaction vial was heated at 230 °C for 72 h and then cooled to room temperature. To the solution was added 1 M Bu₄NF in THF (0.5 mL). After 15 min, the reaction solution was diluted with dichloromethane (300 mL), washed with brine, dried over Na₂SO₄, filtered and evaporated to a yellow syrup, which was purified on a column of silica gel (eluting solvents, ether, 1:1 hexanes-EtOAc, 1:3 hexanes-EtOAc, EtOAc). The following fractions were obtained. The first fraction (eluting with ether) provided unidentified compounds (46.2 mg) that was related to the sugar diene and had Rf values close to compound 136 in TLC. The second fraction (eluting with 1:1 hexanes-EtOAc) gave polymeric materials (45.0 mg), also related to sugar diene. The third fraction (Rf 0.68, EtOAc) was evaporated to give an off-white solid product (58.2 mg), which was demonstrated by its ¹H-NMR spectrum to be a single diastereomer from the exo-addition reaction. The off-white solid product was washed with ether to give a white crystalline product, which was named as 162a, mp 144-145 °C; [α]D +37.0° (c 0.625, CHCl₃); NMR data (¹H, 500 MHz, C₆D₆): δ 7.37-7.07 (m, 20H, 4CH₂Ph), 5.82 (d, 1H, JNH,2' 8.8 Hz, N-
H), 5.13 (dd, 1H, J\textsubscript{2',3'} 7.9 Hz, J\textsubscript{3',4'} 6.2 Hz, H-3'), 4.99 (t, 1H, J\textsubscript{4',5'} 6.2 Hz, H-4'), 4.93, 4.90, 4.79, 4.62, 4.52 and 4.50 (6d, 6H, 3CH\textsubscript{2}Ph), 4.41 (ddd, 1H, J\textsubscript{1',2'} 4.2 Hz, H-2'), 4.38 (m, 3H, CH\textsubscript{2}Ph and H-6'a), 4.16 (m, 2H, H-1' and H-6'b), 4.11 (ddd, 1H, J\textsubscript{1''',2''} 5.9 Hz, J\textsubscript{1''',7'S} 12.1 Hz, J\textsubscript{1'',7'R} 2.6 Hz, H-1''), 3.93 (ddd, 1H, J\textsubscript{5',6'a} 7.3 Hz, J\textsubscript{5',6'b} 3.5 Hz, H-5'), 3.84 (t, 1H, J\textsubscript{2'',3''} = J\textsubscript{3'',4''} 8.7 Hz, H-3''), 3.74-3.68 (m, 5H, H-2'', H-4'', H-5'', H-6''a and H-6''b), 3.47 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 2.71 (dd, 1H, J\textsubscript{6a,5} 2.7 Hz, J\textsubscript{6a,6a} 14.4 Hz, H-6a), 2.64 (dd, 1H, J\textsubscript{2a,3} 3.0 Hz, J\textsubscript{2a,2a} 14.3 Hz, H-2a), 2.41 (m, 1H, H-3), 2.18 (t, 1H, J\textsubscript{3,4} = J\textsubscript{4,5} 10.8 Hz, H-4), 2.14 (m, 1H, H-5), 1.97 (m, 1H, H-7'S), 1.96 (s, 3H, COCH\textsubscript{3}), 1.78 (dd, 1H, J\textsubscript{6a,5} 12.2 Hz, H-6a), 1.77 (dd, 1H, J\textsubscript{2a,3} 12.8 Hz, H-2a), 1.67, 1.60 and 1.59 (3s, 3X3H, 3COCH\textsubscript{3}), 1.55 (m, 2H, H-7'R and H-7'R), 1.39 (dt, J\textsubscript{1',7'S} = J\textsubscript{5,7'S} 7.8 Hz, J\textsubscript{7'S,7'R} 14.4 Hz, H-7'S); (\textsuperscript{13}C, 75 MHz, CDCl\textsubscript{3}): 8 207.34 (C-1), 174.59 (CO\textsubscript{2}Me), 170.88, 170.35, 169.47 and 168.70 (3O\textsubscript{2}CCH\textsubscript{3}), NHOCC\textsubscript{3}), 138.54, 138.14, 138.02 and 137.82, 128.39, 128.28, 128.24, 127.96, 127.85, 127.80, 127.76, 127.71, 127.69, 127.53, 127.51 and 127.44 (aromatic carbons), 82.21, 79.65, 77.72, 75.30, 74.83, 73.41, 73.37, 71.55, 71.19, 70.02, 69.82, 69.17, 68.55, 67.33, 61.15, 54.52, 51.99, 49.99, 45.97, 43.93, 37.99, 35.15, 33.21, 28.92, 22.99 (NHOCC\textsubscript{3}), 20.73, 20.66 and 20.62 (3O\textsubscript{2}CCH\textsubscript{3}); MS: m/z 1037 (M + 2H)+, 1036 (M+H)+, 994 (M + H - CH\textsubscript{2}CO)+, 976 (M + H - HOAc)+, 928 (M - OCH\textsubscript{2}Ph)+, 886 (M - OCH\textsubscript{2}Ph -CH\textsubscript{2}CO)+.

Anal. Calc for C\textsubscript{58}H\textsubscript{69}NO\textsubscript{16} (1036.174): C, 67.23; H, 6.71; N, 1.35.

Found: C, 67.20; H, 6.75; N, 1.35.

The fourth fraction (R\textsubscript{F} 0.57, EtOAc) was evaporated to a white solid product (55.0 mg), which was demonstrated by \textsuperscript{1}H-NMR to be another single diastereomer from the exo-addition reaction-mode. The white solid product was recrystallized from 2:1 hexanes–EtOAc to give a white crystalline product, which
was named as 162b, mp 164–166 °C; [α]D +70.6° (c 0.25, CHCl₃); NMR data
(¹H, 500 MHz, C₆D₆): δ7.37–7.08 (m, 20H, 4CH₂Ph), 5.69 (d, 1H, J₉H,₂ 8.8 Hz, N-H), 5.19 (dd, 1H, J₂',₃', 7.8 Hz, J₃',₄' 6.4 Hz, H-3'), 4.99 (t, 1H, J₄',₅' 6.4 Hz, H-4'), 4.92–4.34 (8d, 8H, 4CH₂Ph), 4.49 (dd, 1H, J₁',₂' 4.3 Hz, H-2'), 4.34 (m, 2H, H-1' and H-6'a), 4.20 (dd, 1H, J₅',₆'b 3.1 Hz, J₆'a,₆'b 12.1 Hz, H-6'b), 3.96 (m, 2H, H-5' and H-1''), 3.75–3.63 (m, 5H, H-3'', H-4'', H-5'', H-6''a and H-6''b), 3.58 (dd, 1H, J₁'',₂'' 5.9 Hz, J₂'',₃'' 9.3 Hz, H-2''), 3.39 (s, 3H, OCH₃), 3.02 (dd, 1H, J₂',₃', 2.6 Hz, J₂',₂', 14.4 Hz, H-2'a), 2.55 (dd 1H, J₆'e,₅' 2.5 Hz, J₆'e,₆'a 14.0 Hz, H-6'e), 2.34 (m, 1H, H-5), 2.25 (l, 1H, J₃',₄' = J₄',₅' 10.8 Hz, H-4), 2.19 (m, 1H, H-3), 1.91 (s, 3H, COCH₃), 1.87 (dd, 1H, J₂a,₃ 11.5 Hz, H-2a), 1.84 (m, 1H, H-7'R), 1.79 (dd, 1H, J₆'a,₅' 13.3 Hz, H-6'a), 1.73 (m, 1H, H-7'R), 1.65, 1.60 and 1.56 (3s, 3X3H, 3COCH₃), 1.54 (m, 1H, H-7'S), 1.24 (ddd, J₇'R,₇'S 14.2 Hz, J₁',₇'S 9.2 Hz, J₅',₇'S 2.7 Hz, H-7'S); (¹³C, 75 MHz, CDCl₃): δ 207.51 (C-1), 174.54 (CO₂CH₃), 170.86, 170.58, 169.50 and 168.81 (3O₂CCH₃), NHOCCH₃), 138.45, 137.98 and 137.80, 128.37, 128.28, 128.10, 127.82, 127.79, 127.75, 127.70, 127.62, 127.58, 127.54 and 127.44 (aromatic carbons), 81.87, 79.48, 77.66, 75.21, 74.89, 74.05, 73.46, 72.94, 71.67, 70.58, 69.81, 68.68, 67.58, 67.10, 61.24, 54.61, 51.68, 50.57, 45.78, 43.89, 39.59, 35.33, 31.25, 28.61, 23.04 (NHOCCH₃), 20.76, 20.65 and 20.61 (3O₂CCH₃); MS: m/z 1036 (M + H)⁺, 1004 (M - OMe)⁺, 994 (M + H - CH₂CO)⁺, 976 (M + H - HCO₂Me)⁺, 928 (M - OCH₂Ph)⁺, 886 (M - OCH₂Ph - CH₂CO)⁺, 796 (M + H - CH₂Ph - OCH₂Ph - CH₂CO)⁺.


Found: C, 67.65; H, 6.75; N, 1.32.
The fifth fraction (eluting with EtOAc) gave unidentified compounds (114.0 mg), related to the sugar dienophile. No endo-addition products were detected.
BIBLIOGRAPHY


