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Synthesis of Those Sectors of Saccharomicin A and B Containing Saccharosamine and the Discovery of a Novel 4-H-1,3-Oxazine Synthesis

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Doctor of Philosophy

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By

Bradley R. Balthaser
B.S., University of Pittsburgh, 2003

Advisor: Frank E. McDonald

An Abstract of
A dissertation submitted to the Faculty of the Graduate School of Emory University in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
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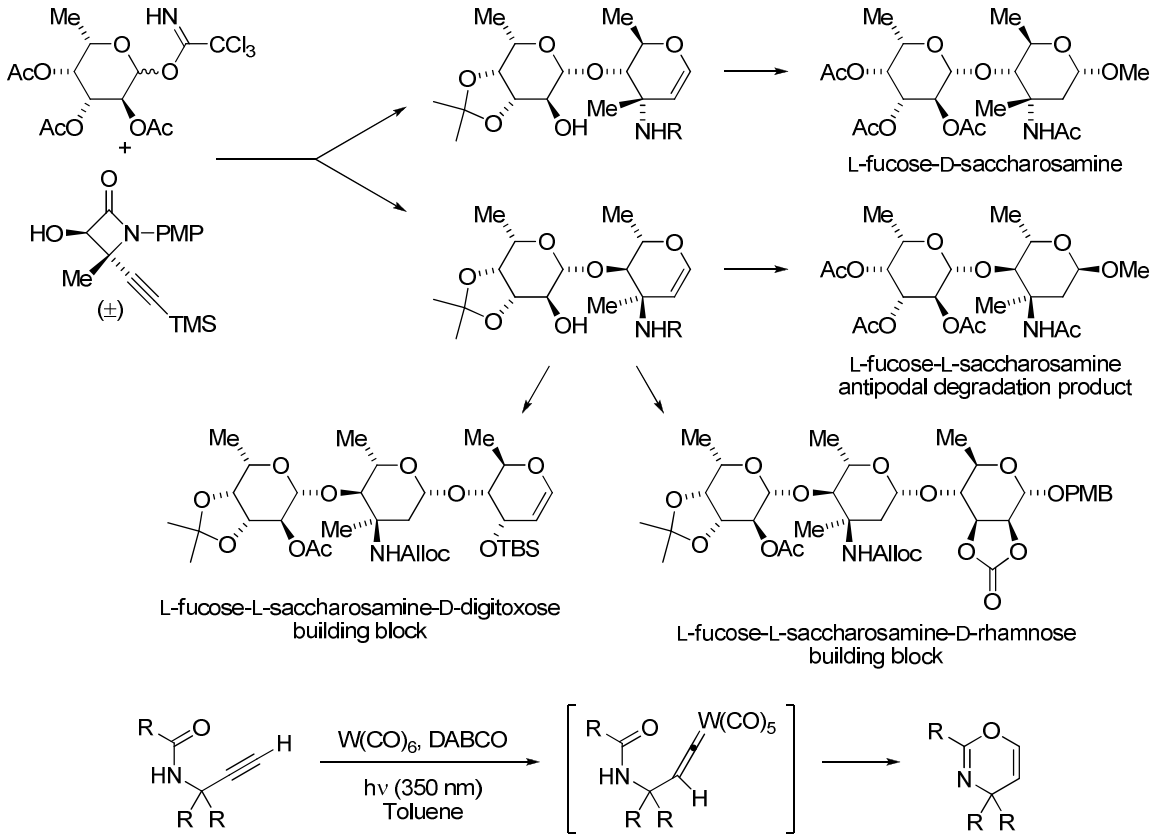
Abstract

Synthesis of Those Sectors of Saccharomicin A and B Containing Saccharosamine and the Discovery of a Novel 4-H-1,3-Oxazine Synthesis

By Bradley R. Balthaser

Saccharomicin A and B are heptadecaglycosides which have been found to possess significant antibiotic activity against a wide array of Gram-positive and Gram-Negative bacteria. These structures possess several interesting structural features and are a composite of five deoxy sugars, including the rare amino sugar saccharosamine.

The synthesis of those sectors of the saccharomicins which contain saccharosamine has been accomplished. Glycosylation of a racemic β-lactam with a fucosyl trichloroimidate provided the congested linkage of the C4-position of saccharosamine. Ring opening and functionalization of β-lactam moiety provided a key alkyne alcohol intermediate. A tungsten-catalyzed cycloisomerization of alkyne alcohols to glycals developed by our group was then use to provide fucosyl-saccharosamine glycal key intermediates, of which three analogues were ultimately produced. The racemic nature of the β-lactam moiety allowed the L-fucose-D-saccharosamine and the L-fucose-L-saccharosamine motifs to be accessed by a divergent route. Manipulation of each disaccharide to its peracetylated form allowed comparison to a degradation product from saccharomicin B, for which the peracetylated L-fucose-L-saccharosamine analogue was found to match as the antipode.



The L-fucosyl-L-saccharosamine glycal intermediate provided the opportunity for an extremely efficient Brønsted acid-promoted glycosylation to be carried out with appropriately functionalized glycosyl acceptors. This process provided access to digitoxose and rhamnose-affixed trisaccharides in 92% and 93% yield respectively. The syntheses of these trisaccharides were carried out such that the protecting group of the terminal fucosyl unit was orthogonal to the reducing end of each analogue, such that each compound might serve as a building block for further studies.

During the course of these studies, an unexpected tungsten-catalyzed cycloisomerization of propargyl amides to 4-H-1,3-oxazines was discovered. Methods for the construction of these oxazines are rare, and the isomerization

represented a novel, and more mild methodology than those previously reported. Preliminary investigations into the scope of this transformation were undertaken.

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Finally, my graduate career would not have been complete without my friends in and out of the department, and my family. To my parents and grandparents, thank you for all of your love, support and patience. My wonderful friends Scott Margeson, Rebecca Booth-Fox, Greg Osisek, Kelly Welch, Jen Sorrells, and Ana Alcaraz have been wonderful sources of support and happiness over the years. I am honored and grateful to call them my friends. Anil Mehta has also been a source of guidance and friendship; I still owe him a beer. Most importantly, to Shana Topp and Stella, thank you for always being there for me and making these past years so wonderful.

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Abbreviations

Ac	acetyl
ADME	absorption, distribution, metabolism, excretion
AIBN	azobisisobutyrlnitrile
Alloc	alloxycarbonyl
app	apparent
aq	aqueous
t-BuOOH	*tert*-butylhydroperoxide
n-BuLi	*n*-butyllithium
Bz	benzoyl
CAN	ammonium cerium nitrate
Cat	catalytic
CDI	1,1´-carbonyldiimidazole
CoA	coenzyme A
COSY	homonuclear correlation spectroscopy
CSA	(+)-camphor-10-sulfonic acid
d	doublet
DCE	1,2-dichloroethane
dig	digitoxose
DIBAL-H	diisobutylaluminum hydride
DMAP	*N,N*-dimetylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
epi	4-*epi*-vancosamine
Equiv	equivalent
EtOAc	ethylacetate
fuc	fucose
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectroscopy
LA	lewis acid

m	multiplet
mmol	millimole
MS	molecular sieves
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PPTs	pyridinium *p*-tolunenesulfonate
Py	pyridine
q	quartet
rha	rhamnose
rt	room temperature
s	singlet
sac	saccharosamine
Sat	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilane
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	toluene

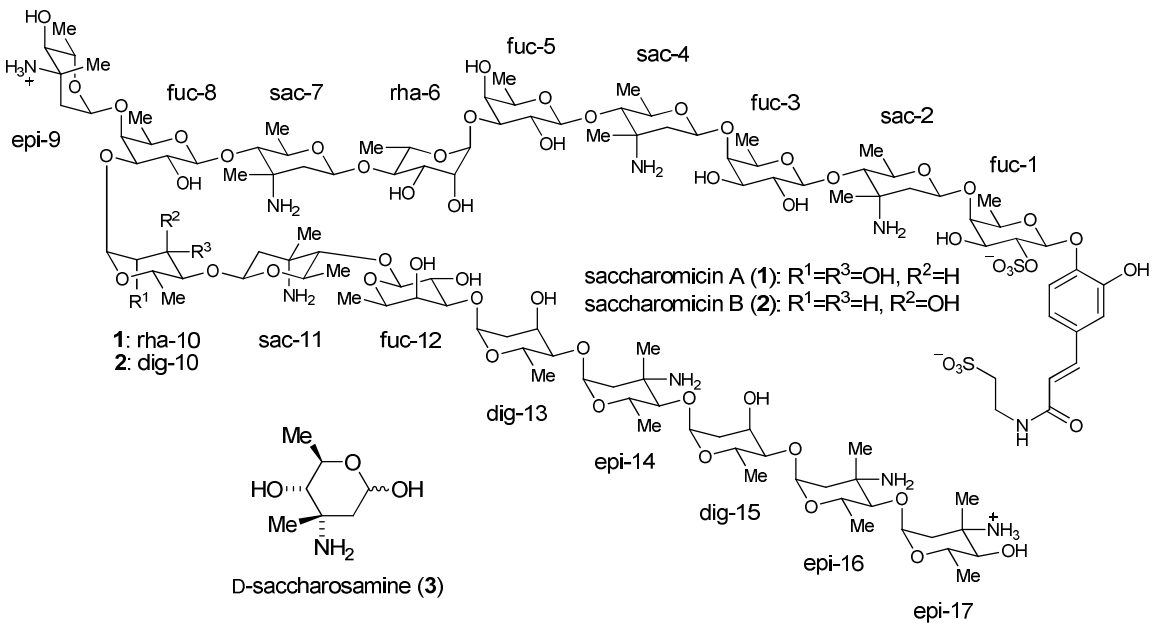
Synthesis of Those Sectors of Saccharomicin A and B Containing Saccharosamine and the Discovery of a Novel 4-H-1,3-Oxazine Synthesis.

1. Background and Introduction

Carbohydrates involved in a large number of biological processes including signal transduction for protein regulation and protein trafficking, as well as cellular and viral recognition events.[1,2] Fertility, inflammation, development, and the immune system are affected by glycosides, and disruption of glycoside expression has been linked to a number of diseases.[3] Elucidating carbohydrate interactions within biological systems is an extremely complicated task, and a great deal of research has been oriented toward understanding these interactions.[1,2] Similarly, the synthesis of carbohydrates presents a challenging platform for the investigation of synthetic methodologies.

Sugars are incorporated into an enormous array of natural structures such as secondary metabolites, many of which possess significant pharmacological activity, including several used as antibiotics.[4,5] Included in this list are the saccharomicins (figure 1.1, see also section 1.2), which are oligosaccharide secondary metabolites isolated from the actinobacteria *Saccharothrix espanaensis*, and found to possess novel antibiotic activity.[6,7] Contained within both natural products is the rare amino sugar saccharosamine. The synthetic studies directed at those domains of the saccharomicins which contain saccharosamine represent the main focus of this dissertation.

Figure 1.1: Saccharomicins A and B with D-Saccharosamine



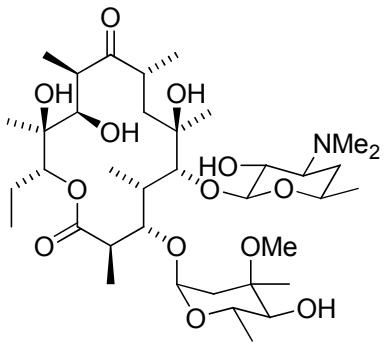
1.1. Selected amino sugar containing antibiotics

The saccharomicins are a recent addition to a litany of other amino sugar-containing glycosides which possess antibiotic activity, and it is worth briefly surveying this class of molecules. While antibiotics can function through several mechanisms, the discussion herein is limited to those amino sugar containing glycosides which disrupt ribosomal function, or degrade the bacterial cell wall.

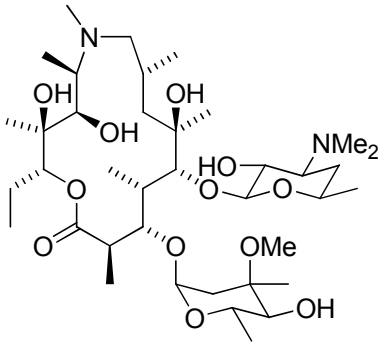
Disruption of ribosomal function by these types of antibiotics can occur in a number of ways.[4] A binding interaction with the ribosome might cause dissociation of tRNA or mistranslation of mRNA, either of which can lead to the early release of the growing peptide chain. Coordination of an antibiotic to a ribosomal subunit can also prevent the ribosome initiation complex from assembling. Each of these mechanisms sufficiently hinders protein synthesis such that cell death occurs.

Compounds which are thought to interact with the bacterial ribosome include macrolide antibiotics such as erythromycin A (figure 1.2),[4,8,9] which are often used clinically to treat patients allergic to β-lactam based antibiotics. The mechanism of action for erythromycin A is proposed to bind the 23S ribosomal subunit in many Gram-positive bacteria. This perturbation leads to the dissociation of peptidyl tRNA, which in turn causes early release of the growing peptide chain from the ribosome. Several variants of erythromycin A have been synthesized, many of which show improved pharmacokinetics and greater activity against Gram-negative bacteria.[4,8]

Figure 1.2: Macrolide Antibiotics Erythromycin A and Azithromycin



erythromycin A (**4**)



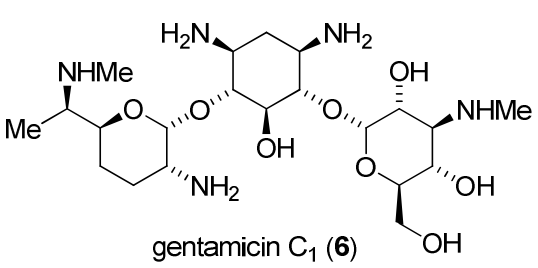
azithromycin (**5**)

Structurally, macrolide antibiotics consist of a polyketide macrocyclic core which is glycosylated in one or more positions, frequently with the amino sugar desosamine.[8] The precise role of the amino sugar functionality is not known, but it has been observed that presence of these pyranosides is essential for *in vivo* activity.[8] It may be that the sugars greatly affect the pharmacokinetic properties of the macrolides (ADME), increasing water solubility and thus bioavailability. Protonated under physiological conditions, the basic nitrogen has also been

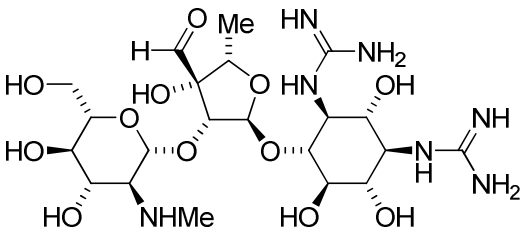
linked to active transport of the macrolide into the cell,[10] and might also be involved in recognizing the negatively charged ribosomal backbone.

Aminoglycoside antibiotics such as gentamicin C_1, represent another class of amino sugar-containing antibiotics which act upon the ribosome (figure 1.3).[11,12] Clinically, the aminoglycosides are administered as a mixture of congeners and are effective against a wide array of bacteria, including many Gram-negative strains. The analogue streptomycin is even used as a treatment against tuberculosis.[13] These antibacterial glycosides work by binding to the A-site of the prokaryotic ribosome, which causes mistranslation of the mRNA, and in turn the early termination of forming peptide chains.

Figure 1.3: Aminoglycosides Gentamicin C_1 and Streptomycin



gentamicin C_1 (**6**)



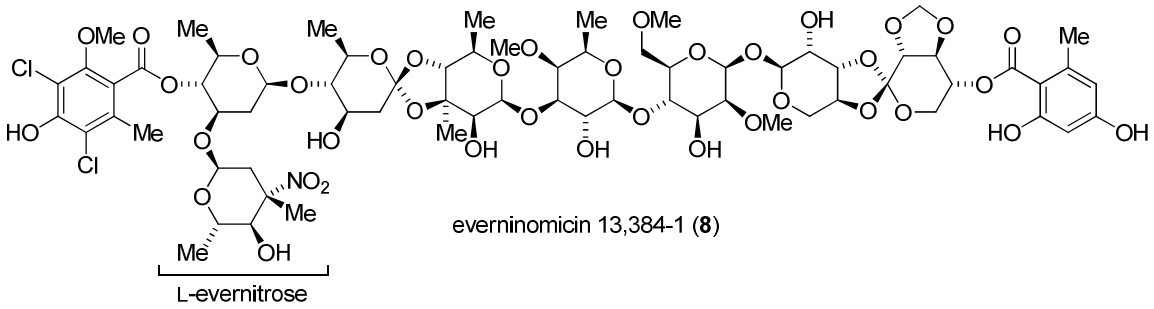
streptomycin (**7**)

Members of this family contain an aminocyclitol core which is appended with a variety of sugars, the majority of which are amino sugars.[11,12] The amino sugar moieties are protonated under physiological conditions, and ultimately aid in binding to the negatively charged backbone of ribosomal RNA.

Everninomicin is a member of the orthosomycin class of compounds which also targets the ribosome (Figure 1.4).[14-16] Competition between everninomicin and other ribosomal inhibiting antibiotics was not observed, indicating a novel binding site. Everninomicin binds the 50s ribosomal site, later

refined to the 23s rRNA portion. Rather than disrupting peptide synthesis by causing early termination of the growing peptide chain, everninomicin acts by preventing assembly of the ribosomal initiation complex.[17,18]

Figure 1.4: Everninomicin 13,384-1

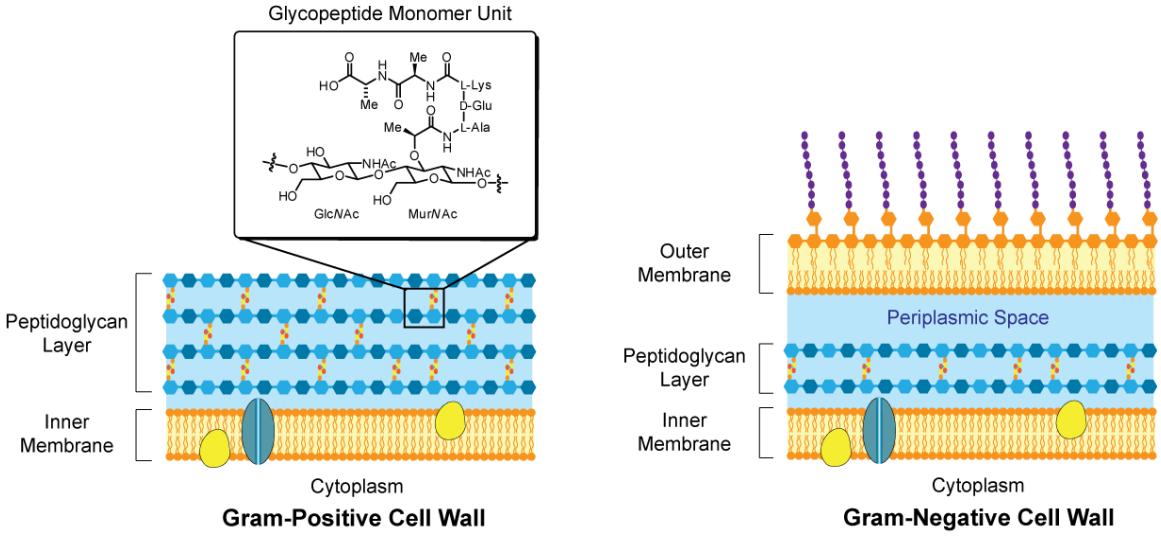


Unlike the macrolide and aminoglycoside antibiotics, everninomicin is primarily a carbohydrate-based composite of several deoxy sugars and orthoester linkages. It also possesses the intriguing C3-quaternary-C3-nitro sugar evernitrose, which is the nitro analogue of 4-*epi*-vancosamine found in the saccharomicins. The precise role of the nitro sugar in not known.

Some amino sugar-affixed antibiotics target not the ribosome, but instead the cell wall. The bacterial cell membrane possesses a structure known as the peptidoglycan layer, which is not found in mammalian cells. Both Gram-positive and Gram-negative bacteria have a peptidoglycan layer, differing principally in their thickness and location (figure 1.5).[4] In Gram-positive bacteria, the peptidoglycan layer is a thick, multilayer matrix forming the outer surface of the bacteria. The peptidoglycan layer in Gram-negative bacteria is smaller than in Gram-positive species, and is contained within the periplasmic space between two phospholipid bilayers. Consistent of a carbohydrate backbone, most commonly made of an *N*-acetylglucosamine (Glc*N*Ac), *N*-acetylmuramic acid

(Mur*N*Ac) disaccharide unit which is polymerized by glycosyltransferase enzymes.[4] Appended to the D-lactoyl moiety of muramic acid is a peptide sequence is cross-linked by transpeptidases.[19,20] The highly cross-linked structure of the peptidoglycan ultimately results in a very stable structure, which affords the bacteria with its overall shape, as well as protection from lysis due to changes in osmotic pressure.

Figure 1.5: Gram-Negative and Gram-Positive Bacterial Cell Walls with Peptidoglycan Monomer Structure

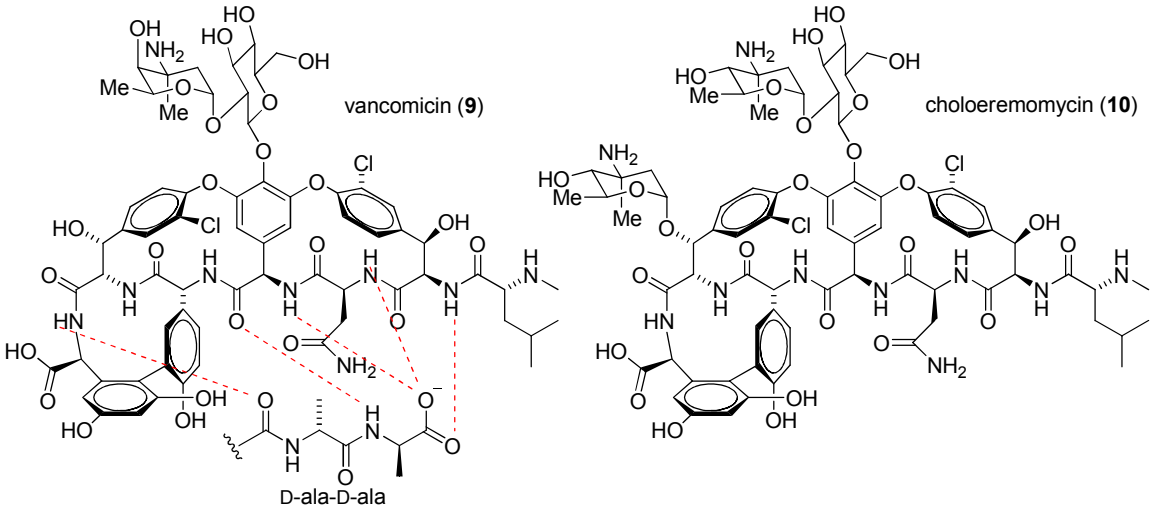


Antibiotics which target the peptidoglycan layer manage to significantly compromise the structure such that cell lysis occurs. Activity can occur through inhibition of transpeptidases or sequestration of their substrate to prevent adequate crosslinking, while polymerization of the carbohydrate backbone is prevented by inhibiting glycoyltranserferases.[4] Some compounds might also cause pore formation.

The best known amino sugar-containing antibiotics acting upon the peptidoglycan layer is Vancomycin (figure 1.6).[19,21] Vancomycin is one of only

two glycopeptide antibiotics approved for clinical use, and is active against a large number of Gram-positive bacteria. The mechanism of antibiotic activity stems from a high affinity between the vancomycin aglycone and the D-Ala-D-Ala terminus of the peptidoglycan monomer. The transpeptidase substrate is effectively sequestered, which inhibits cross linking and leads to a compromised peptidoglycan matrix. Vancomycin also dimerizes in solution, which heightens the binding affinity through allosteric interactions, as well as decreasing the entropic price of binding to the peptidoglycan.[19,22] Resistance to vancomycin stems from strains which have altered their peptidoglycan terminal D-alanine to a D-serine or D-lactate.

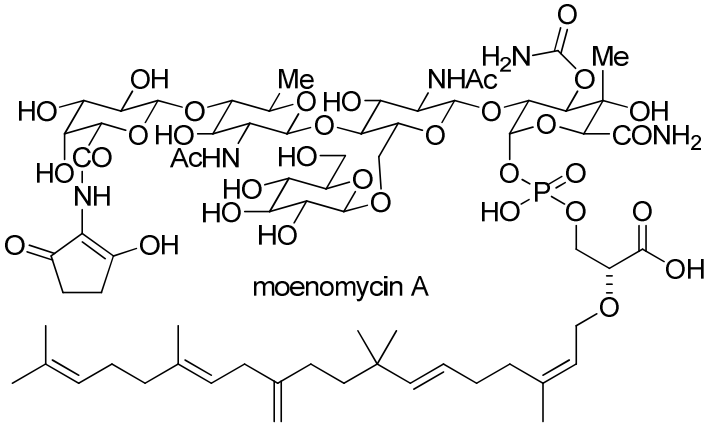
Figure 1.6: Vancomycin and Choloeremomycin; Binding of Vancosamine to Substrate is Shown



The peptide core of vancomycin is a composite of seven peptides with a highly cross-linked structure, especially through its aromatic functionalities. Appended to the 4-OH-PheGly$_4$ oxygen is a vancosaminyl-α-1,2-glucosyl disaccharide.[19,21] The role of the carbohydrate portion of vancomycin is not fully

understood. The pyranosides do aid in keeping the hydrophobic aglycone portion water soluble, though their role appears to be more important than just solubility. Removal of the sugars results in an aglycone core that is still effective *in vitro*, but whose *in vivo* activity is significantly reduced.[4,23] Some NMR studies have indicated that the carbohydrates help maintain the bioactive conformation of the aglycone portion, and they have also been implicated in promoting the dimerization of vancomycin.[22,24] A number of vancomycin analogues have been made which vary in the number, identity, and position of pendant sugars. Examples such as choloeremomycin have actually been found to have increased potency, as well as regained activity against vancomycin resistant strains of Gram-positive bacteria.[25]

Figure 1.7: Antibiotic Moenomycin A



Another amino sugar containing antibiotic which disrupts the peptidoglycan layer is moenomycin A (1.7).[26-28] Instead of preventing the cross-linking of peptides in the matrix, moenomycin inhibits the glycosyltransferases, preventing the carbohydrate backbone of the peptidoglycan layer from being polymerized. The glucosamine in moenomycin does not simply improve the pharmacokinetics

of the molecule, but is actually the active portion of the antibiotic, acting as an effective glycosyltransferase substrate mimic.

From the antibiotics covered here, it is clear that the amino sugar moieties in these compounds provide a variety of important interactions, including increased solubility, maintaining active conformations, and aiding in substrate recognition. Understanding the chemistry involved in both the construction of these pyranosides, and their incorporation into complex structures is valuable. The saccharomicins provide an excellent platform for investigating the connections of two rare and structurally complex amino sugars; 4-*epi*-vancosamine and saccharosamine.

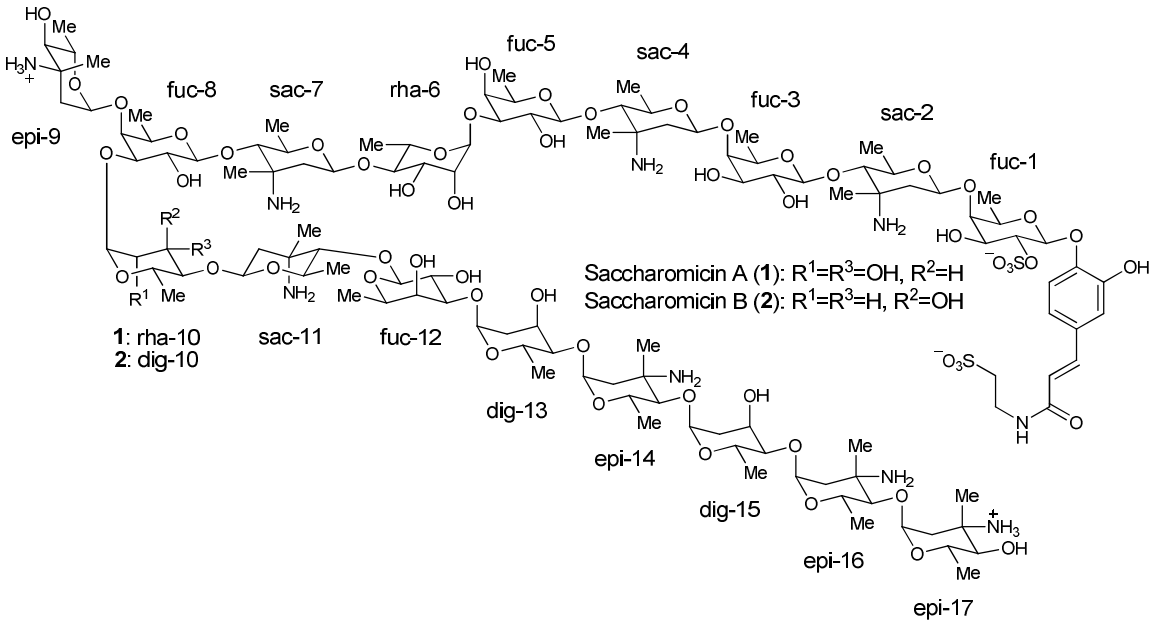
1.2. Saccharomicins A and B

1.2.1. Biogenesis and Antibiotic Activity of the Saccharomicins

Saccharomicins A (**1**) and B (**2**) are heterogeneous heptadecaglycosides that were first reported in 1998 as an isolate from *Saccharothrix espanaensis*, a gram-positive member of the actinomycetes group of bacteria (figure 1.8).[6] Investigations into the biological activity of the saccharomicins demonstrated them to be effective antibiotics for a variety of gram-positive and gram-negative bacteria.[7] Both oligosaccharides possess activity against an array of antibiotic-resistant cultures, whereas enterococcus cultures are slightly less affected (MIC range 0.25 – 16 μg/mL) than staphylococci strains (MIC range <0.12 – 0.5 μg/mL). It is notable that both vancomycin-susceptible and vancomycin-resistant strains are equally affected. While mouse models have shown the

saccharomicins' ability to protect against pathogens at a level comparable to vancomycin, the therapeutic window is too narrow for clinical consideration.

Figure 1.8: Saccharomicins A and B

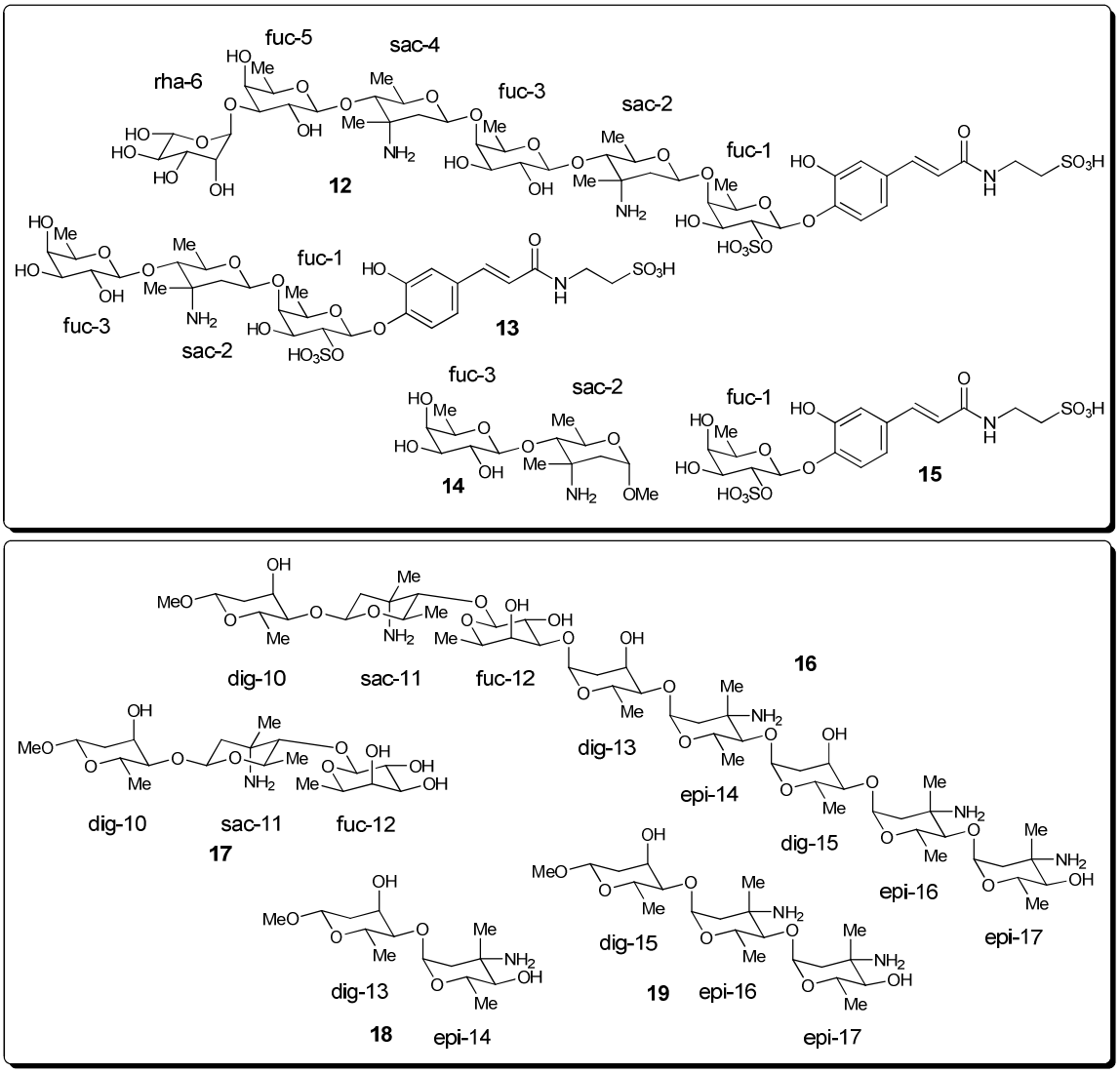


The exact mechanism of activity of the saccharomicins remains unclear, though they have been observed to disrupt the bacterial cell wall. Studies designed to measure membrane damage for both *E. coli imp* and human red blood cells revealed leakage of intracellular potassium from *E. coli* (indicating cell lysis), while no hemolysis was observed in the human cells. Direct disruption of the peptidoglycan layer might have therefore occurred, perhaps through pore formation. Studies following the uptake and incorporation of radiolabeled thymidine, uridine, and amino acids were also carried out. In all cases, incorporation of the labeled compounds fell off at a parallel rate compared to their uptake, again indicating that the saccharomicins acted up the bacterial membrane.

1.2.2. Characterization of the Saccharomicins and the Enantiomeric Identity of Its Pyranosides

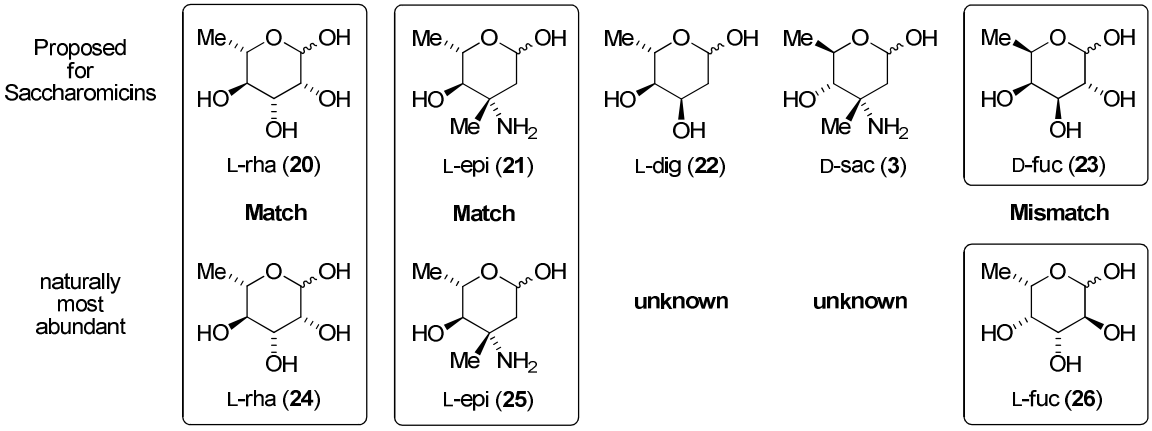
Investigation of their structures revealed the saccharomicins to be heptadecasaccharides with largely linear oligomer structures, with one branching event at the 8-sugar. The characterizations of saccharomicin A and B were carried out using a degradation procedure in which a host of fragments were obtained (figure 1.9). A variety of analytical techniques including NMR, x-ray

Figure 1.9: Representative Degradation Products from the Saccharomicins



analysis and mass spectrometry were employed to assess the structure the parent compounds and their fragments.[6,29] Mass spectrometry, along with HMBC and NOESY NMR experiments, were particularly valuable in mapping out the sequence of the carbohydrates. The 2D-NMR correlations also revealed the regiochemistry of the glycosidic bonds. Comparison of saccharomicin A and B showed that their structures were highly conserved between both natural products. The compounds were found to vary only at pyranose 10, where saccharomicin A consisted of rhamnose, and saccharomicin B contained digitoxose.

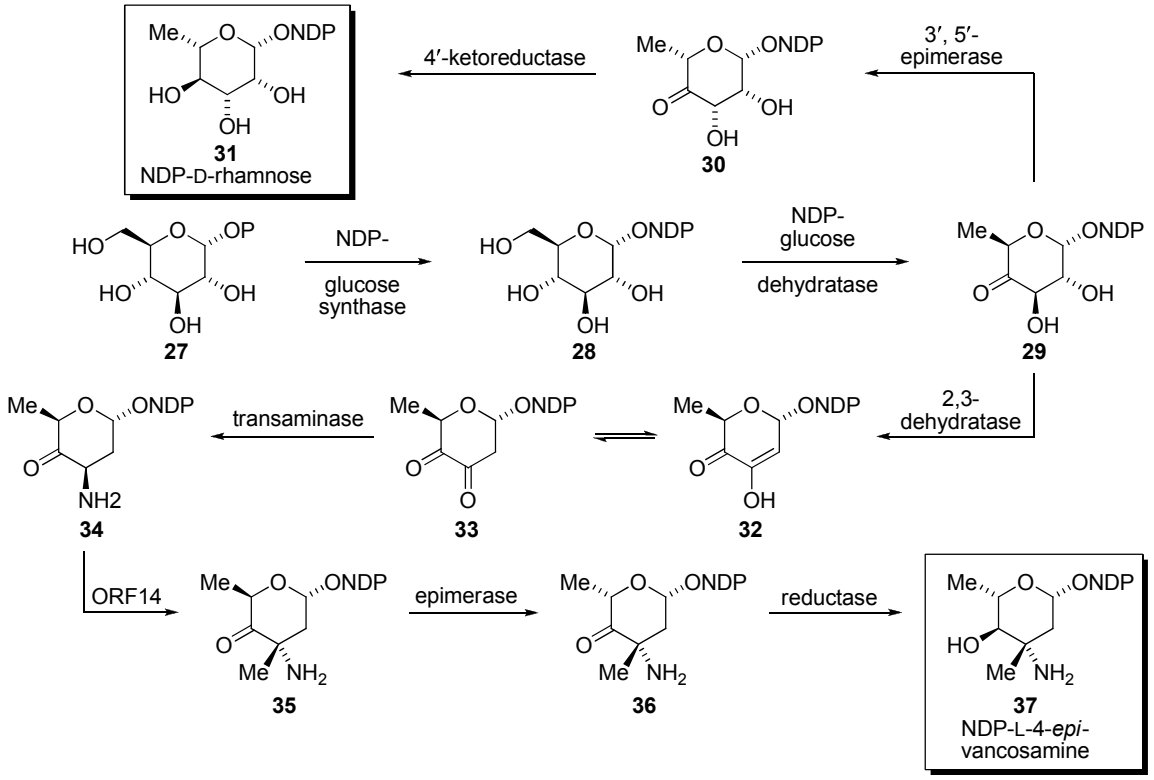
Figure 1.10: The Proposed Enantiomeric Identity of the Saccharomicin Sugars



Five different 6-deoxy-sugars were found to populate the saccharomicins: rhamnose, digitoxose, fucose, 4-*epi*-vancosamine, and saccharosamine. While the stereochemistry of each pyranoside was established, the absolute stereochemistry and the relative stereochemistry between pyranosides could not be determined. The authors of the seminal paper had therefore attributed the sugars to be L-rhamnose, L-digitoxose, D-fucose, D-saccharosamine, and L-4-*epi*-vancosamine, stating that these assignments were based on the naturally most

abundant enantiomers of each sugar (Figure 1.10). While this approach was inherently logical, there were a few potential, if unavoidable discrepancies in the assignments.

Scheme 1.1: Biosynthesis of L-Rhamnose and L-4-epi-Vancosamine



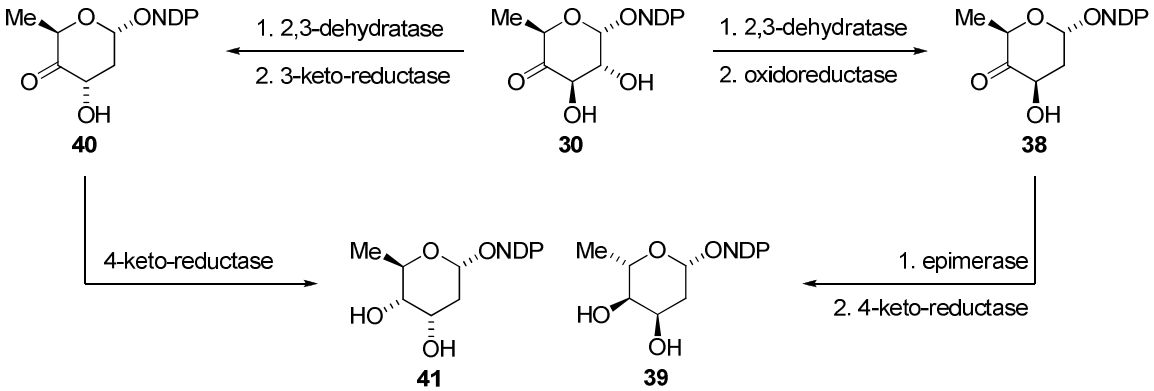
The assignment of rhamnose and 4-*epi*-vancosamine as their L-forms is likely correct. Both L-rhamnose and L-4-*epi*-vancosamine are the naturally most abundant forms in actinomycetes,[30] and the biosynthesis of both pyranosides in this class of bacteria are known (scheme 1.1).[31-33] While not found in humans, L-rhamnose is commonly produced in plants and is a common component of bacterial cell walls. The D-form is known, but is far more rare, having been primarily observed in the LPS of gram-negative bacteria.[30] First reported in

1988,[34] L-4-*epi*-vancosamine is a somewhat rare sugar, but known occurrences of the L-form greatly outnumber those of the D-form.[25,33,35]

The assignment made in the saccharomicins of D-fucose is not of the biologically most prevalent enantioform. L-Fucose is found in both eukaryotes and prokaryotes, and as a component of bacterial cell walls in both Gram-positive and Gram-negative strains.[30] While D-fucose has been observed in bacteria *O*-antigens, the number of cases is comparatively small.[30,36] D-Fucose is therefore a possible candidate, but from a statistical perspective, L-fucose might be the more likely form found in the saccharomicins.

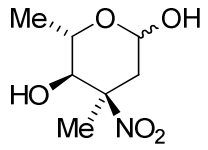
Unlike rhamnose, fucose, and 4-epi-vancosamine, neither enantioform of digitoxose is necessarily more abundant in the actinomycetes group of bacteria. Both L- and D-digitoxose have been identified in actinomycetes secondary metabolites and their biosyntheses stem from a common intermediate (scheme 1.2).[37,38] However, there is no clear indication which form might be more common. In plants, L-digitoxose does predominate,[39] but there is no evidence that this trend would extend to *Saccharothrix espanaensis*.

Scheme 1.2: Biosynthesis of L- and D-Digitoxose

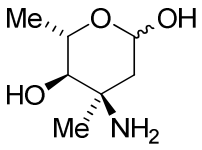


The prevalent enantiomeric form of saccharosamine is entirely unknown, as the saccharomicins are the first instance in which this pyranoside has been reported. The only hint at what enantioform saccharosamine might possess comes from structurally related L-decilonitrose (figure 1.11). Decilonitrose, which is found in cororubicin[40] and decilorubicin,[41] has been established as the L-form.[42] However, the biosynthesis for neither decilonitrose nor saccharomicin is known, and no correlation between the two can be drawn with any certainty.

Figure 1.11: L-Decilonitrose and L-Saccharosamine



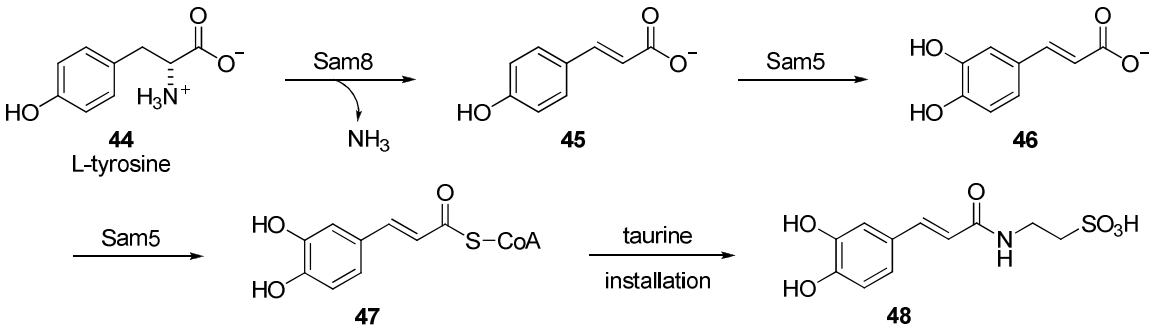
L-decilonitrose (**42**)



L-saccharosamine (**43**)

The only portion of the saccharomicins for which a biosynthesis has been investigated is the unique aglycone structure (scheme 1.3).[43] The dihydroxycinnamoyl moiety stems from L-tyrosine, and several enzymes involved in this transformation have been identified. It remains unclear how the taurine moiety is incorporated.

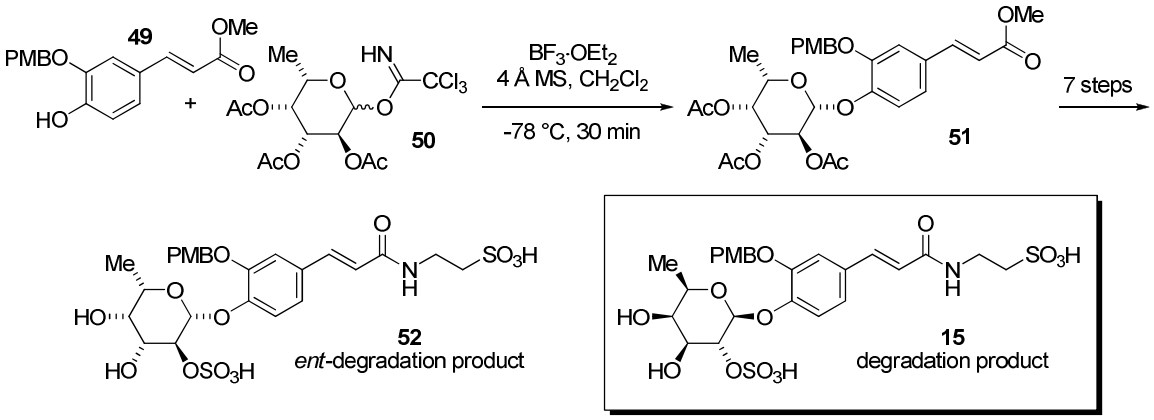
Scheme 1.3: Biosynthesis of the Saccharomicin A and B Aglycone



1.2.3. Previous synthetic work on the saccharomicins

Synthetic work geared directly at the saccharomicins has thus far been limited to the assembly of the fucose-aglycone portion (scheme 1.4).[44] This synthesis met several important goals including formation of the β-glycosidic bond between fucose and the aglycone, as well as installation of the sensitive C2-sulfate and terminal taurine units. Comparison of glycoside **52** and degradation product **15** also established the enantiomeric identity of fucose as the D-form within the saccharomicins, at least for the terminal sugar-1 fucose. This was an interesting observation considering the rarity of D-fucose in nature.

Scheme 1.4: Synthesis of the Saccharomicin *ent*-Fucose-Aglycone Conjugate



1.3. Synthetic work relevant to the saccharosamine-containing sectors of the saccharomicins

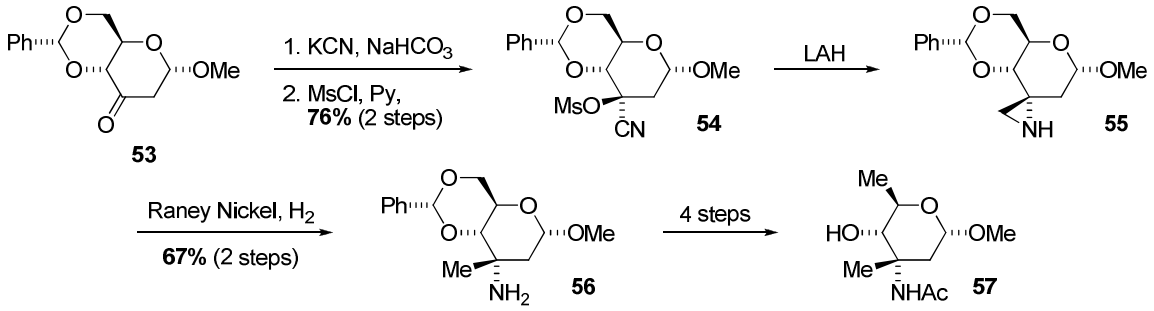
1.3.1. Previous syntheses and glycosylations of saccharosamine

While the saccharomicins are the only reported natural products which are known to contain saccharosamine, there is a surprising amount of synthetic work which accesses this pyranoside already reported in the literature. Due its structural relation to both decilonitrose and vancosamine, several groups have

either passed through saccharosamine, or constructed it as an analogue. The key synthetic steps of these syntheses frequently focus on setting the C3-quanternary stereochemistry.

The first saccharosamine synthesis was reported in 1979 by Thang *et al.* during their work on vancosamine (scheme 1.5).[45] Starting from known keto-pyranoside **53** (prepared in a two-step elimination process from α-methyl-D-mannose)[46] the C3-quaternary center was established by addition of cyanide (diastereoselectivity not reported), and subsequent displacement of mesylate under reductive conditions to provide aziridine **55**. Reductive opening of the aziridine provided the C3-quaternary center, and intermediate **56** was carried on to *N*-acyl-D-saccharosamine glycoside **57** through a four-step process.

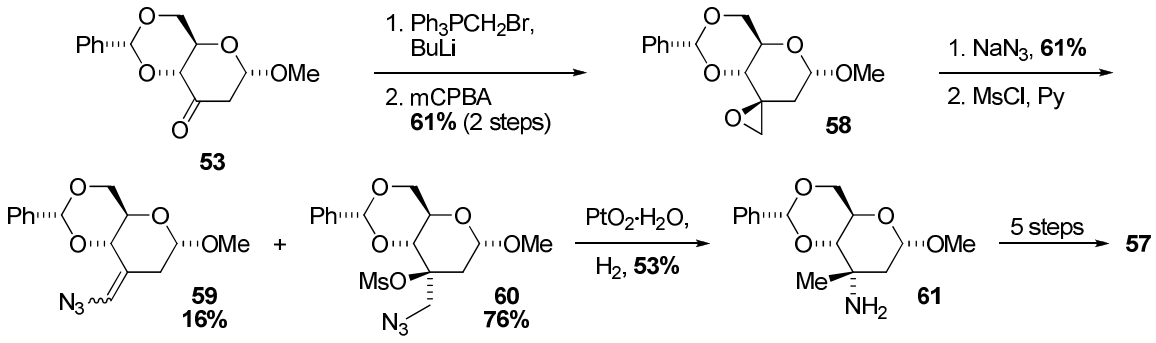
Scheme 1.5: The First Synthesis of Saccharosamine



A few years later, Brimacombe's D-rubranitrose synthesis provided a second route which utilized ketone **53** and passed through an aziridine intermediate (scheme 1.6).[47] After converting **53** to known epoxide **58**[48], azide addition followed by mesylate formation provided both azide **60** and the elimination product **59**. Hydrogenation of compound **60** then provided the desired C3-stereochemistry, presumably passing through aziridine **55** as an intermediate formed *in situ*. A very similar synthesis was eventually reported by

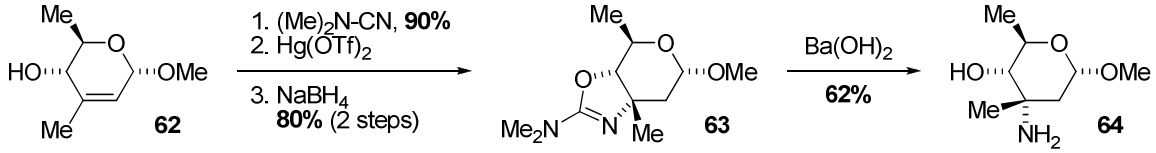
Sato *et al.*, in which ketone **53** was brought up from glucose instead of mannose.[49]

Scheme 1.6: A Modified Saccharosamine Synthesis



An alternative method to introduce nitrogen at the C3-position would be to utilize a pendant nucleophile attached to the C4-hydroxyl. Such an approach has been carried out (scheme 1.7).[50] From known allylic alcohol **62** (prepared in seven steps from D-mannose)[51] a dimethylaminoimidate was formed and then cyclized using mercuric trifluoroacetate. The mercurial intermediate was reduced providing oxazoline **63**. Deprotection under basic conditions provided α-methyl saccharosamine **64**.

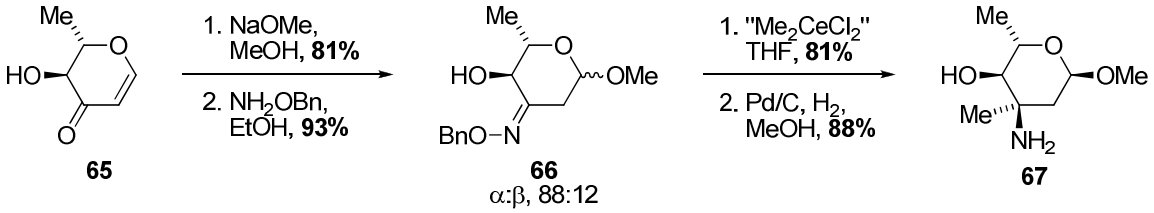
Scheme 1.7: Installation of the C3-Amine by Direction of the C4-Functionality



In 1993, Scharf *et al.* reported the first L-saccharosamine synthesis while in route to decilonitrose (scheme 1.8).[52] Base catalyzed Michael addition to known ketone **65**[53] followed by condensation with *O*-benzylhyroxylamine provided oximino derivative **66**. Methylation followed by concomitant debenzylation and reductive N-O cleavage provided α-methyl-L-saccharosamine

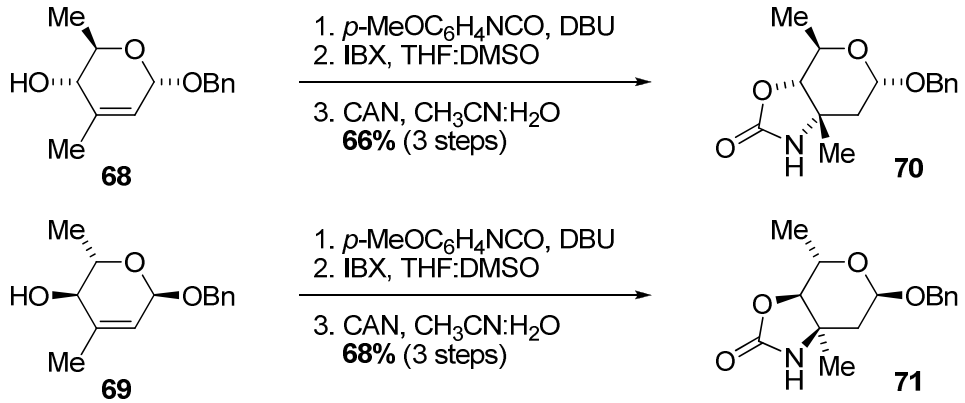
glycoside **67**. In the same body of work, the D-saccharosamine analogue was also prepared, but through a much longer synthetic route from D-mannose (15 steps).

Scheme 1.8: The First L-Saccharosamine Synthesis

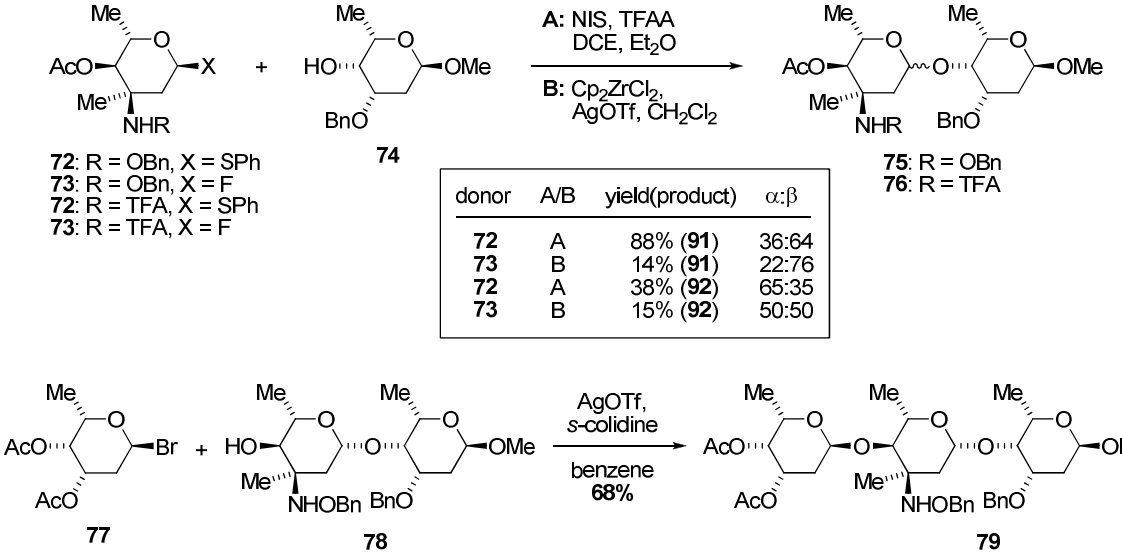


In 2000, a novel preparation of both L- and D-saccharosamine analogues by an IBX mediated process appeared (scheme 1.9).[54] Carbamate formation from **68** and **69** with *p*-methoxyphenyl isocyanate, followed by a posited single electron transfer cyclization promoted by IBX formed the desired quaternary center. Removal of the aromatic functionality by CAN oxidation provided both carbamate protected saccharosamine analogues **70** and **71**. While the syntheses of the allylic alcohols were not reported, Takahashi *et al*. have since developed an efficient synthesis of the allylic alcohols from either (*R*) or (*S*)-furfuryl alcohol.[55]

Scheme 1.9: IBX Promoted Synthesis of Saccharosamine



Scheme 1.10: Previous Glycosylations of the Saccharosamine Motif



donor	A/B	yield(product)	α:β
72	A	88% (**91**)	36:64
73	B	14% (**91**)	22:76
72	A	38% (**92**)	65:35
73	B	15% (**92**)	50:50

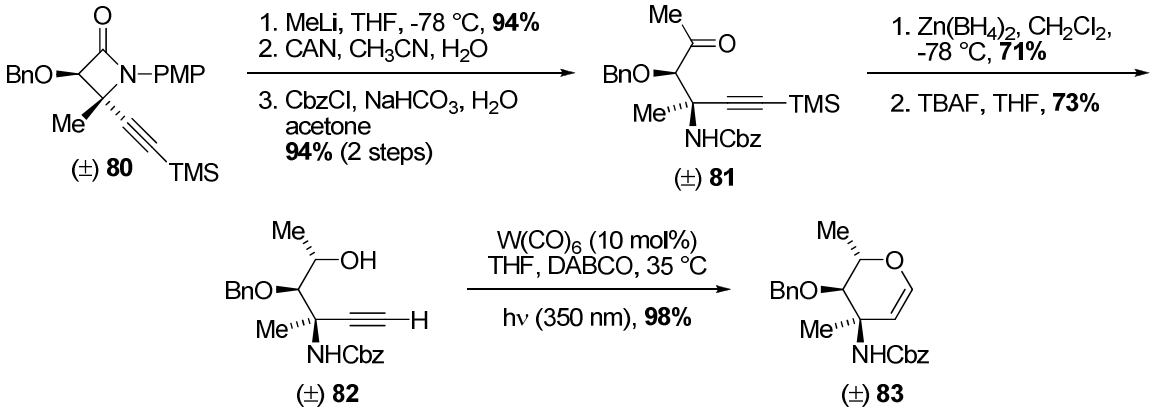
There is very little synthetic work investigating the glycosidic linkages involving in the saccharosamine motif. What little work there is stems from the synthesis of cororubicin carried out by Giulliano *et al.*[56] As a glycosyl donor, both the saccharosamine-glycosyl fluoride **73** and sulfide **72** (prepared using Scharf's method) were coupled with a C2-deoxy-fucose analogue **74** (scheme 1.10). The glycosyl fluorides coupled only in low yields, and while the sulfides provided higher conversion, the selectivity was not high. Oddly, the trifluoroacetamide seemed to favor the α-glycosyl linkage. In the end, use of sulfide **72** provided the β-glycoside in modest, but synthetically useful yields. As a glycosyl acceptor, the only linkage using the saccharosamine motif performed was Koenigs-Knorr glycosylation with relatively unhindered C2-deoxy-fucoside **77** setting the thermodynamically favored α-glycoside **79**.

Of all the syntheses accessing the saccharosamine architecture reported so far, none had accessed a saccharosamine glycal. A glycal analogue would

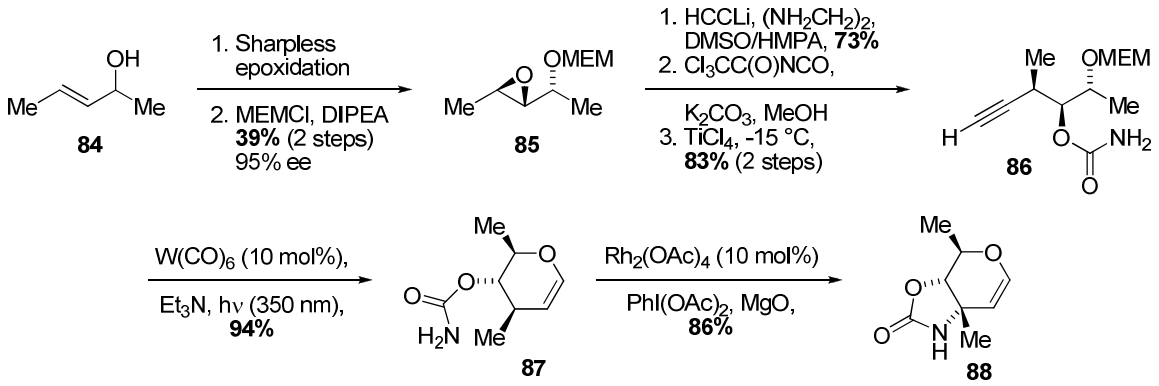
provide the opportunity for a de novo synthesis of saccharosamine, as well as new glycosylation opportunities, important in light of those difficulties experienced previously. In 2002 our research group reported the first saccharosamine glycal synthesis as an extension of our cycloisomerization methodology (scheme 1.11).[57] Ring opening of β-lactam **80**, formed by Staudinger cycloaddition, followed by stereoselective reduction provided alkyne alcohol **82**, which possessed all of the stereocenters found in saccharosamine. A tungsten-catalyzed cycloisomerization (see section 1.3.2.) was then used to provide racemic saccharosamine glycal **83**.

A short time later an enantiopure saccharosamine glycal synthesis was presented by Parker *et al.*, again utilizing our cycloisomerization chemistry (scheme 1.12).[58] A Sharpless asymmetric epoxidation was used to establish the enantiopurity leading to alkyne **86**. After instillation of the urethane functional group, a tungsten-catalyzed cycloisomerization was again used to form glycal **88**. A C-H bond activation protocol then established the C3-quaternary center.

Scheme 1.11: The First Saccharosamine Glycal Synthesis



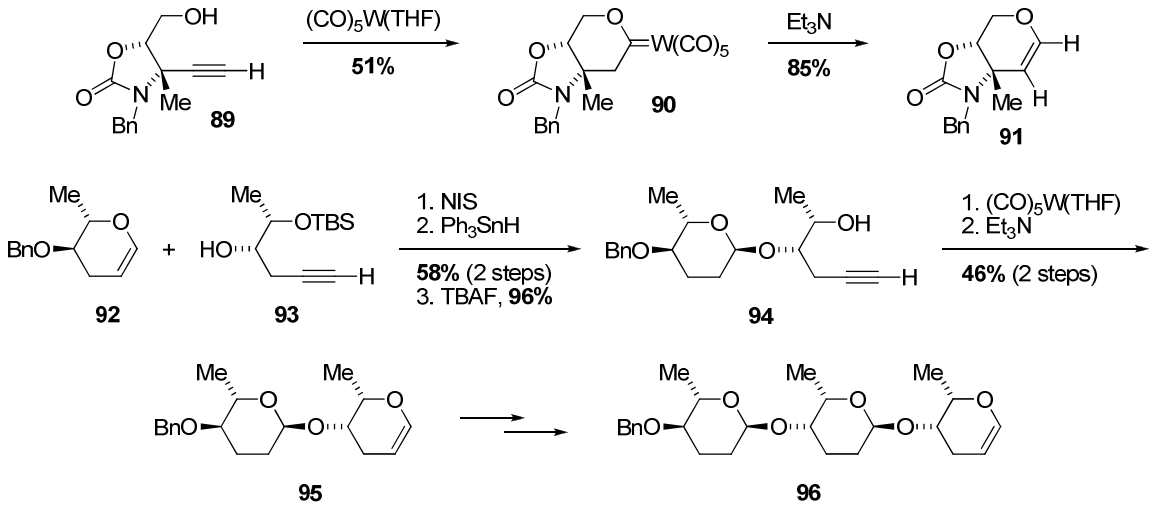
Scheme 1.12: Enantiopure Synthesis of Saccharosamine Glycal



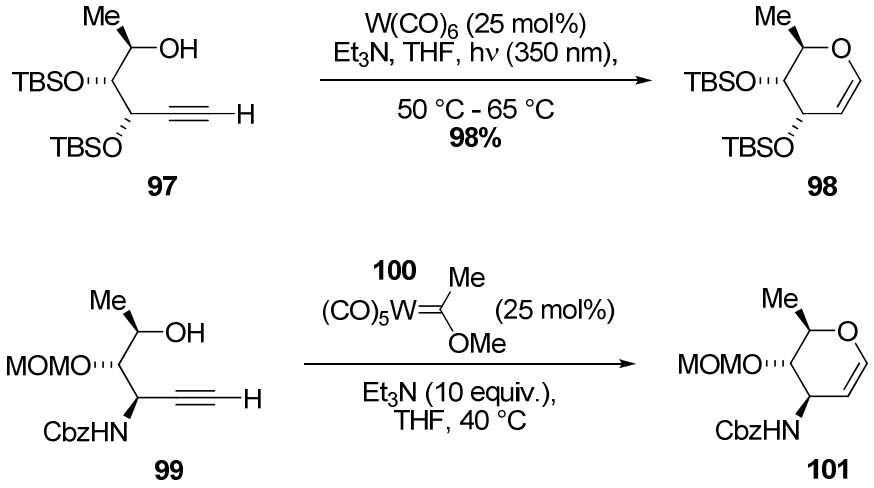
1.3.2. Tungsten Catalyzed Cycloisomerization of Alkyne Alcohols

Several years ago our group discovered a two-step process to form tungsten carbenes from alkyne alcohols, and promote their rearrangement to glycals by addition of a base (scheme 1.13).[59,60] This process proved immediately useful, allowing for the development of a methodology which was used to assemble the L-aculose-α-L-rhodinose-α-L-rhodinosal trisaccharide **96**.[61] This methodology was somewhat limited however, as the yields were not particularly high, and the process required stoichiometric amounts of tungsten.

Scheme 1.13: Early Tungsten-Mediated Cycloisomerization Method

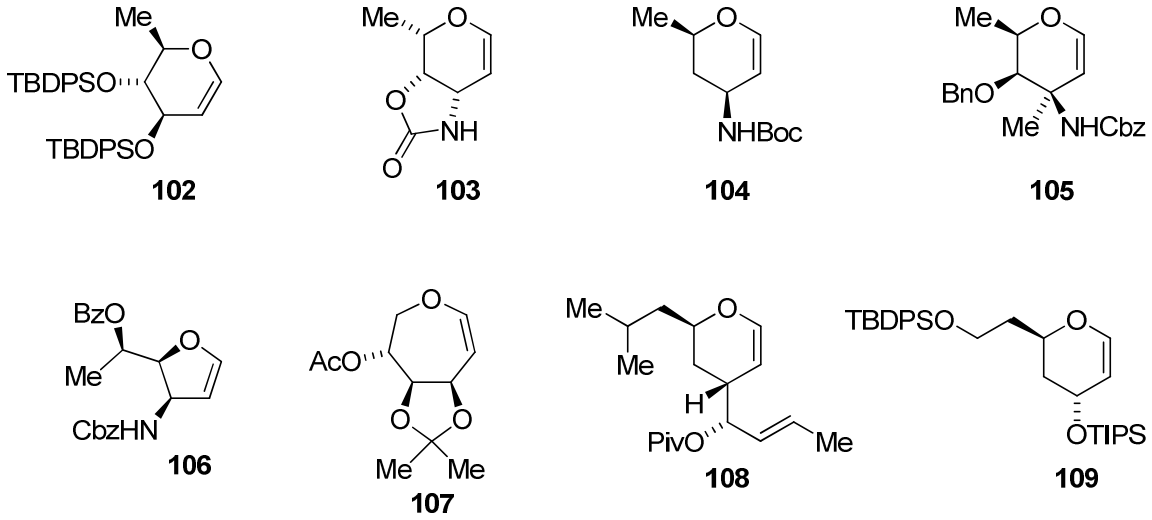


Scheme 1.14: Advent of the Tungsten-Catalyzed Cycloisomerization



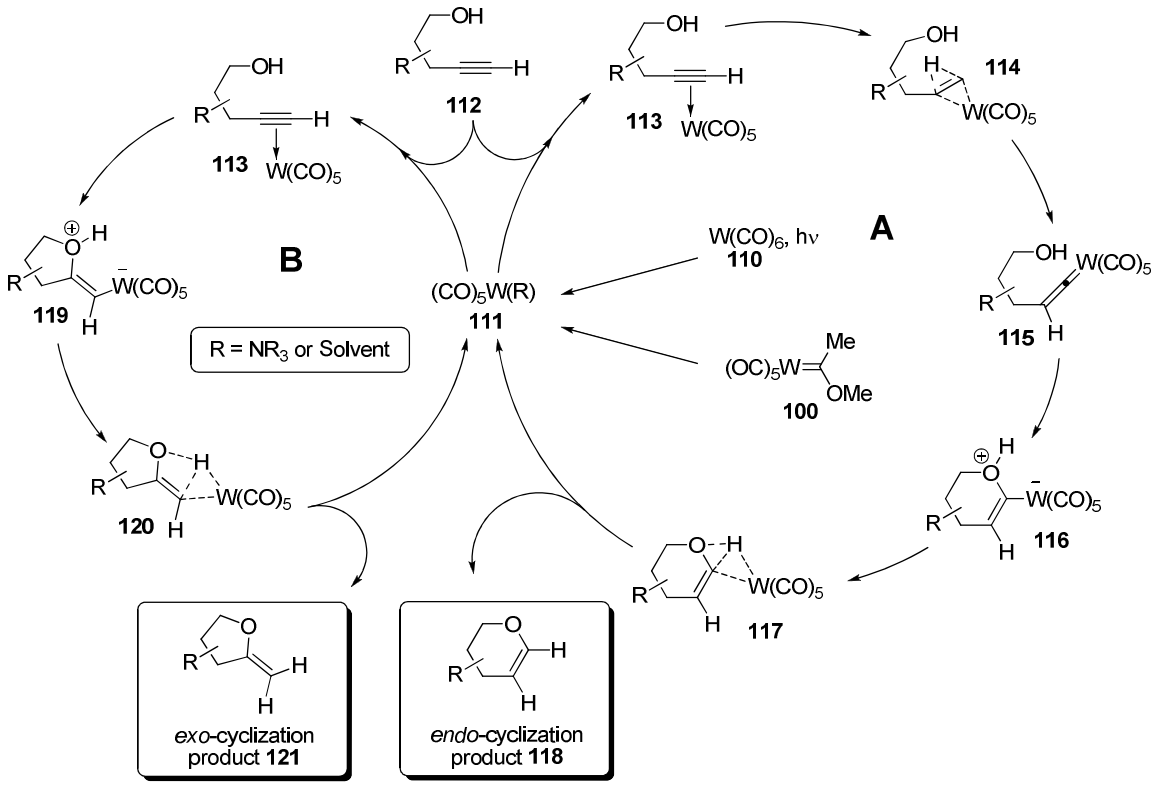
Soon thereafter, major improvements were made by switching from a tungsten-tetrahydrofuran complex, to tungsten hexacarbonyl in the presence of a tertiary amine base as a one pot process (scheme 1.14).[62] This process proved to be vastly more efficient. Tungsten hexacarbonyl, which was activated by 350 nm light, could now be used in catalytic amounts due to the *in situ* formation of glycal from reaction with the amine base present in the reaction mixture. The net result of these changes was a catalytic cycloisomerization process that produced glycals in far higher yields, through a simpler synthetic procedure. Another important advance was the use of pentacarbonyl (methoxymethyl) tungsten carbene catalyst **100**, which allowed the cycloisomerization to be carried without requiring a 350 nm light source.[63] Over the past several years our tungsten-catalyzed cycloisomerization of alkyne alcohols has been utilized by our laboratory and others to prepare a wide array of glycals (figure 1.12).[57,58,62-68]

Figure 1.12: A Selection of Glycals Prepared by the Tungsten-Catalyzed Cycloisomerization Methodology



A combination of results obtained experimentally and several computational analyses has led to a mechanism that is reasonably well understood (scheme 1.15).[69-72] Either precatalyst **100** or **110** first forms the tungsten pentacarbonyl moiety **111**, which then coordinates to the substrate alkyne. A 1,2-migratory shift of the terminal hydrogen then provides a rearranged tungsten vinylidene intermediate **114** (cycle **A**). The 1,2-hydrogen shift is mechanistically supported by deuterium-labeling studies,[73] and computational analyses indicate that this process is the rate determining step for the isomerization.[69,71,72] The vinylidene α-carbon, being highly electrophilic, then undergoes nucleophilic attack from the pendant alcohol five, six, or seven atoms away. The resulting zwitterionic species **116** then undergoes insertion of proton through the same coordination site on tungsten to deliver the endocyclic glycal product, and regenerate the tungsten catalyst. The proton might be delivered by the ethereal oxygen as depicted in **117**, or transfer may occur intermolecularly.

Scheme 1.15: Catalytic Cycle of the Tungsten-Mediated Cycloisomerization of Alkyne Alcohols to Glycals



An alternative route to glycal can also be considered, which more closely resembling the two-step process shown in scheme 13. From **116**, proton transfer to the C2-position would form a tungsten carbene which in turn could be converted to glycal by amine base acting as a proton shuttle. Solvent choice and the stoichiometric ratio of base present in the reaction mixture might influence which proton transfer process is preferred.[70,71]

As an alternative to glycal formation, the tungsten catalyst can also act simply as a Lewis acidic species, prompting a 5-exo cyclization to occur (**119**, cycle **B**). Transfer of proton then results in exocyclic side product and again recycles the tungsten catalyst.

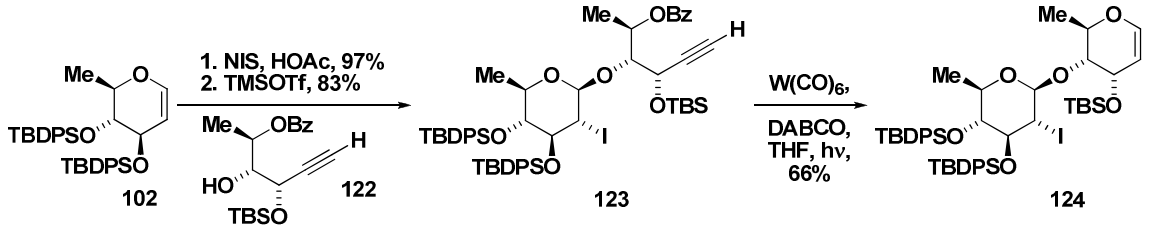
Several factors can influence the reaction outcome (path **A** or **B**) including solvent choice, identity of base, and substrate substitution. The cycloisomerization is frequently compatible with THF, but this solvent sometimes promotes nucleophilic attack of the alcohol, leading to increased amounts of exocyclic product **121**. Switching to a non-ethereal solvent such as toluene often alleviates this problem. The choice of tertiary amine base has also been found to impact the reaction outcome. In general use of 1,4-diazabicyclo[2.2.2]octane (DABCO) favors the endo-cyclic product **118** in the photoactivated system,[74] while triethylamine provides the best results when the Fischer carbene catalyst is used.[63]

Substitution at the propargylic position tends to promote glycal formation over five-membered ring formation.[62] This is presumably due to steric and/or stereoelectronic repulsion between the propargylic substituents and tungsten, which may encourage rearrangement of the metal complex to its more distal vinylidene form. However, substitution at the propargylic position is not necessary, and Barluenga *et al*. have discovered that by reducing the loading of amine base to 2 mol%, glycal formation can still be successfully selected for.[71]

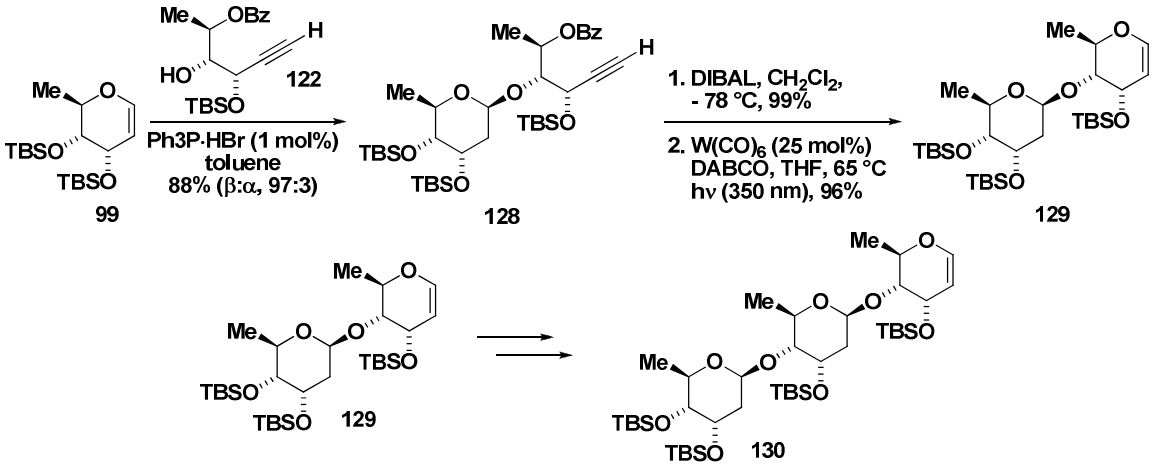
Many glycal-glycosylation methodologies have been developed over the years and the topic is well reviewed.[75-77] Not surprising then, our group has been able to couple our tungsten-catalyzed cycloisomerization process with some of these glycal-glycosylation methods in order to construct a variety of oligosaccharide structures (scheme 1.16). Iodoglycosylation of glycal with an appropriately functionalized alkyne alcohol, followed by an iterative

cycloisomerization has allowed us to assemble several disaccharide units such as **124**.[63,74] Conversion of seven-membered ring glycal **125** to septanoside glycosyl donor **126** allowed the complex septanose trisaccharide **127** to be constructed.[78]

Scheme 1.16: Coupling Our Tungsten-Catalyzed Glycal Methodology



Scheme 1.17: Brønsted Acid-Catalyzed Glycal Glycosylations



An even more efficient process can be imagined for glycosylating C2-deoxy sugars, in which the glycal produced by our cycloisomerization is linked to an appropriate glycosyl acceptor under Brønsted acid-promoted conditions.

Such a process was carried out in our digitoxin synthesis, where a three-step iterative method yielded the digitoxose trisaccharide **130** (scheme 1.17).[62,79] Exploring the utility of our cycloisomerization chemistry in constructing complex oligosaccharide structures remains of interest to our research group, due to the conceptual simplicity of directly preparing 2-deoxyglycosides from glycals and carbohydrate alcohols under catalytic, atom-efficient conditions.

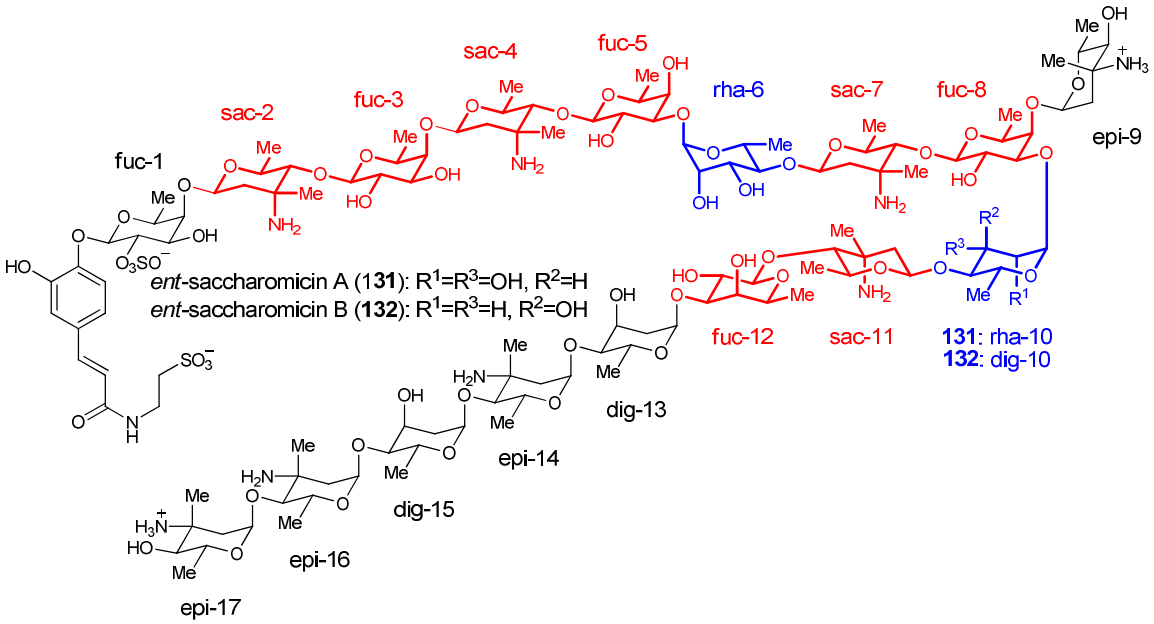
1.4. Retrosynthetic Analysis of the Saccharosamine Containing Segments of Saccharomicin A and B

The synthetic work contained herein was focused on those sectors of saccharomicin A and B relating to saccharosamine and its connections. These segments constitute a large portion of the natural products, reaching from fucose-12 to saccharosamine-2, with the exclusion of *epi*-vancosamine-9 (Figure 1.13). In designing a synthesis for these portions we have chosen to pursue the enantiomeric structure to that proposed for the saccharomicins. This was in keeping with our previous synthetic work on the L-fucosyl-aglycone portion,[44] and would allow us to work with L-fucose which is both the more abundant in nature, and significantly less expensive than D-fucose.

We wished to meet several goals in entering these studies. Firstly, we desired to utilize our tungsten-catalyzed cycloisomerization for the construction of saccharosamine in the context of complex oligosaccharides. We reasoned that a more classical carbohydrate synthesis of this amino-sugar would be cumbersome, and that our cycloisomerization chemistry would allow a more

efficient synthesis. Such a synthesis would extend our glycal methodology to fully heterogeneous oligosaccharides at both the reducing and non-reducing end of the glycal.

Figure 1.13: *ent*-Saccharomicin A and B



Not surprisingly then, we also wished to explore the glycosylation chemistry surrounding saccharosamine. As either a glycosyl donor or glycosyl acceptor, saccharosamine presents challenges in establishing these linkages. On one hand, the steric congestion around the C4-hydroxyl of saccharosamine would make it a reluctant glycosyl acceptor. The inverse problem is present when saccharosamine is used as the glycosyl donor. The β-glycosyl linkages found at the reducing end of saccharosamine are presumably less thermodynamically stable compared to the α-anomer, and would likely need to be accessed as the kinetic product. In carbohydrate synthesis, β-glycosides are often constructed using anchimeric assistance, but for the saccharomicins this method is not an option due to the C2-deoxy center on saccharosamine. Instead

kinetic control would likely rely on effects inherited from the overall conformation of the pyranoside. In addressing these challenging glycosylations we sought to exploit several trends observed in the saccharomicins.

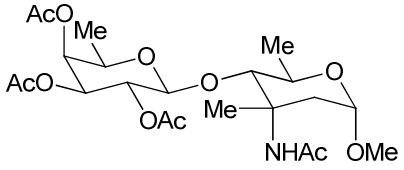
During the characterization of the saccharomicins the fucose-saccharosamine glycosidic linkage was observed to be the most robust of these bonds. In both saccharomicins this linkage appears consistently as the β-glycoside, connected to the C4-hydroxyl of saccharosamine. Therefore, by setting this connection early in our synthesis we would produce a stable disaccharide building block for the assembly of larger segments of the natural products. Because these glycosyl bonds favor the kinetic anomer, the steric bulk of the saccharosaminyl acceptor might lend itself towards forming the β-glycoside.

Controlling the stereochemical outcome at the anomeric position of saccharosamine also posits an attractive opportunity. While glycosylated to a variety of sugars (rhamnose, digitoxose, and fucose) the stereochemistry at the saccharosamine C1-position is again β throughout both natural products. The consistency of the stereochemistry, with a breadth of acceptors, hints that one might indeed be able to take advantage if stereoelectronic effects inherent to saccharosamine to direct the outcome of its glycosylation chemistry.

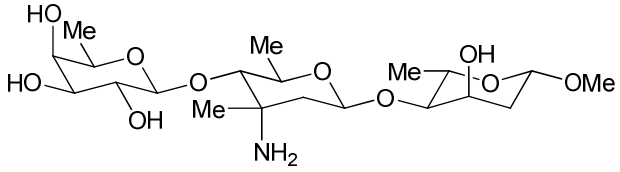
Finally, we required that our synthetic route pass through intermediates which would could serve as building blocks for larger oligosaccharide portions, as well as diverge modestly to secure different saccharomicin degradation products (Figure 1.14). Comparison of our synthetic material to the degradation products

would allow us to assess the relative stereochemistry of each pyranoside as they occur in the saccharomicins. The antipodes **135** and **136** of peracetylated fucose-saccharosamine disaccharide **133**, and related trisaccharide **134** would be targeted for this purpose.

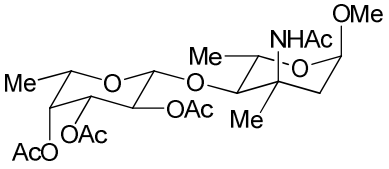
Figure 1.14: Targeted Degradation Products Isolated From the Saccharomicins



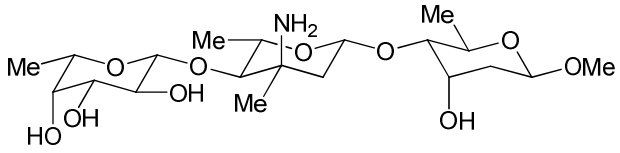
peracetyl-D-fucose-D-saccharosamine (**133**)
degradation product



D-fucose-D-saccharosamine-L-digitoxose (**134**)
degradation product



peracetyl-L-fucose-L-saccharosamine (**135**)

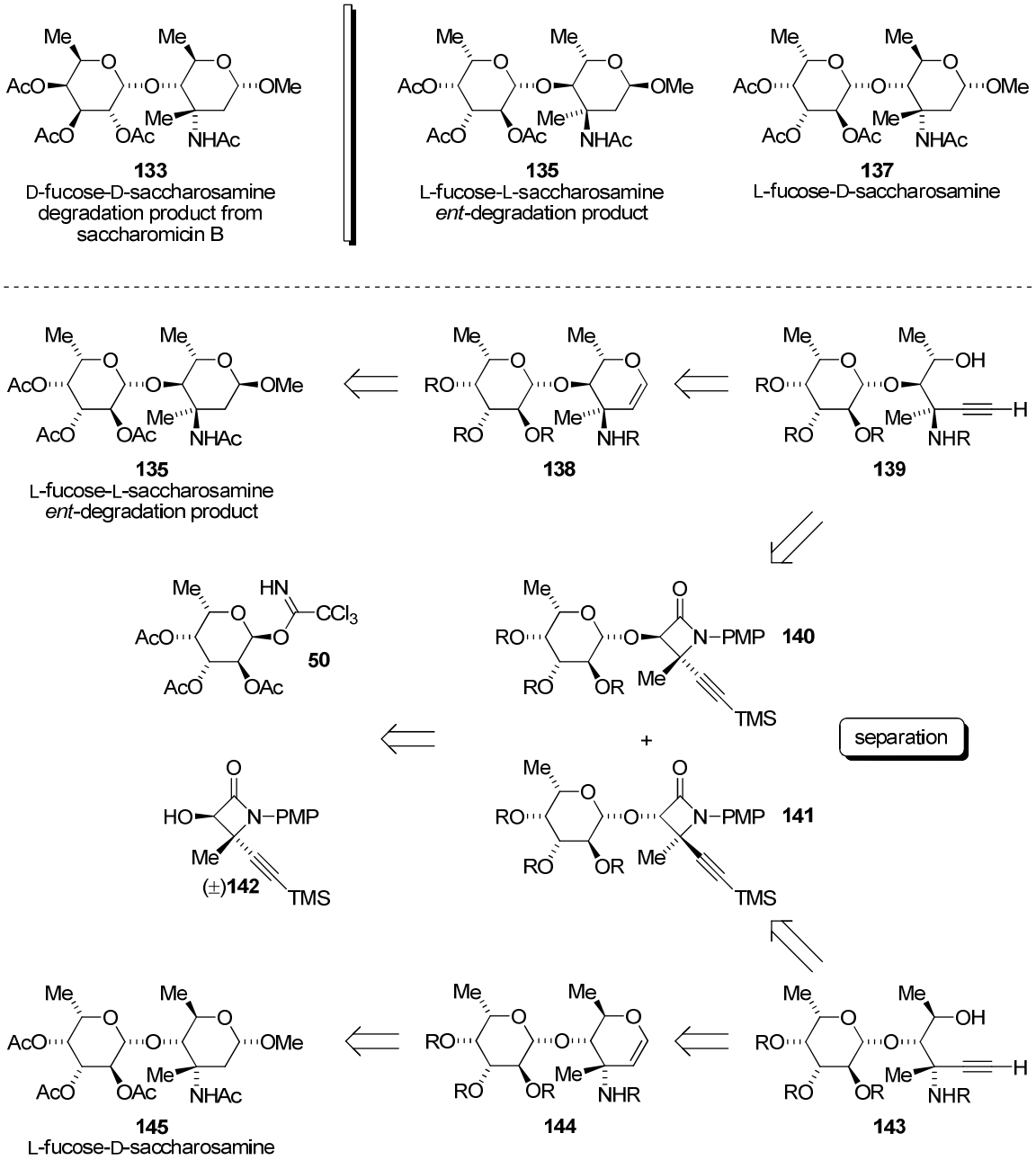


L-fucose-L-saccharosamine-D-digitoxose (**136**)

Disaccharide **135** was an especially attractive preliminary target. The fucosyl-saccharosaminyl unit is repeated four times in each of the saccharomicins (fuc-12 → sac-11, fuc-8 → sac-7, fuc-5 → sac-4, and fuc-3 → sac-2), making it an elementary module for the synthesis of larger oligosaccharides. A glycal intermediate leading to **135** would provide a platform not only for the synthesis of the antipodal degradation product, but could also be redirected for the synthesis of larger oligosaccharides.

As mentioned before, our actual target was not the D-fucose-D-saccharosamine disaccharide **133** reported in the originating saccharomicin paper, but rather the L-fucose-L-saccharosamine enantiomer **135** (Scheme 1.18). We envisioned that the peracetylated sugar would stem from late stage

Scheme 1.18: Retrosynthetic Analysis of L-Fucose-L-Saccharosamine and L-Fucose-D-Saccharosamine Disaccharide Targets



functional group manipulation of a preceding saccharosaminyl glycal **138**. Tungsten-catalyzed cycloisomerization of alkyne alcohol **139** would provide glycal **138**, and the alkyne alcohol would be resultant of ring-opening and

functionalization of fucosyl-β-lactam glycoside **140**. Fucoside **140** would be forged by a Schmidt glycosylation[80,81] of fucosyl trichloroimidate **50**[82] and racemic β-lactam **142**.[57,63]

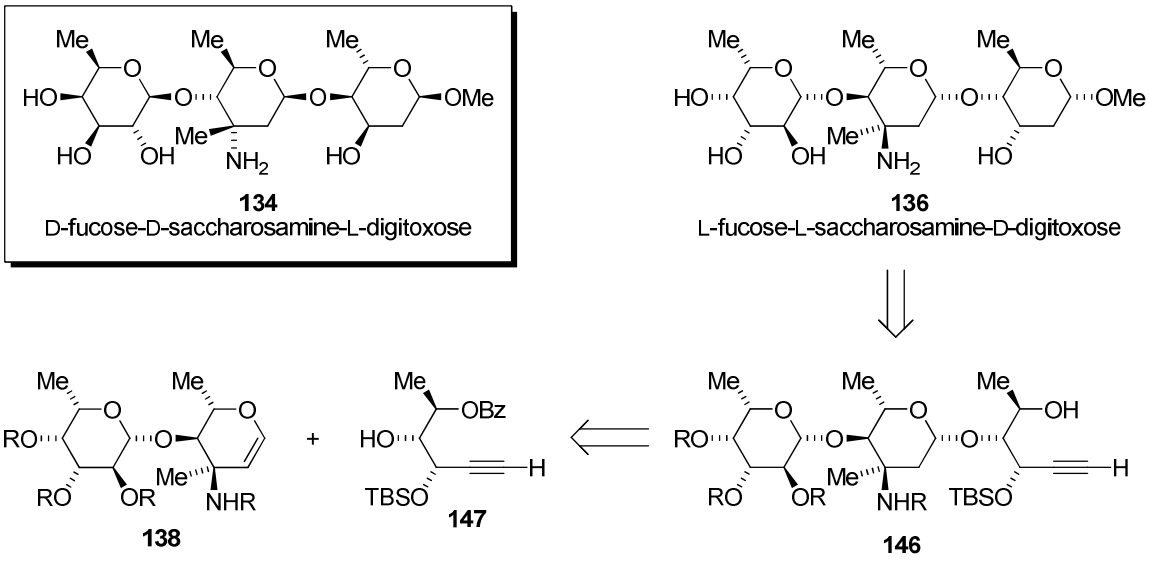
Because the absolute and relative stereochemistry of the saccharomicins was not established, it was important for us to access not only the L,L-disaccharide, but also the L-fucose-D-saccharosamine diastereomer **137**. A divergent synthesis that would produce both disaccharides in tandem would provide a potent crosscheck for the structure of the fucose-saccharosamine degradation product. Such an analysis would be valuable as the spectral data relating to the degradation product was not reported in the original paper, and we did not know what materials would eventually be available for comparison.

Glycosylation of racemic β-lactam **142** would lead to both diastereomer **140** and **141**, and we envisioned using the L-fucosyl moiety to resolve these glycosides. Compound **141** would then be carried forward to peracetyl-L-fucose-D-saccharosamine. Ideally the routes leading to each disaccharide would be largely similar.

We also sought to synthesize the L-fucose-L-saccharosamine-D-digitoxose trisaccharide **136** as an extension of our disaccharide synthesis (scheme 1.19). Trisaccharide **136** would also relate to a degradation product with which it could be compared, and would represent fuc-12 $\rightarrow$ sac-11 $\rightarrow$ dig-10 in saccharomicin B. The synthesis of **136** would be finalized in a similar manner as the disaccharide unit, in that the digitoxose pyranoside would be formed late stage by a cycloisomerization of its alkyne alcohol precursor. Adduct **146** would arrive

from glycosylation of previously constructed saccharosaminyl-glycal **138** and glycosyl acceptor **147**.[62] Connecting these two compounds would provide us with the opportunity to explore a Brønsted acid-promoted glycosylation of saccharosaminyl glycal **138**. We hoped to identify the kinetic product from such a reaction, and ultimately to establish the β-glycosidic linkage in a controlled process.

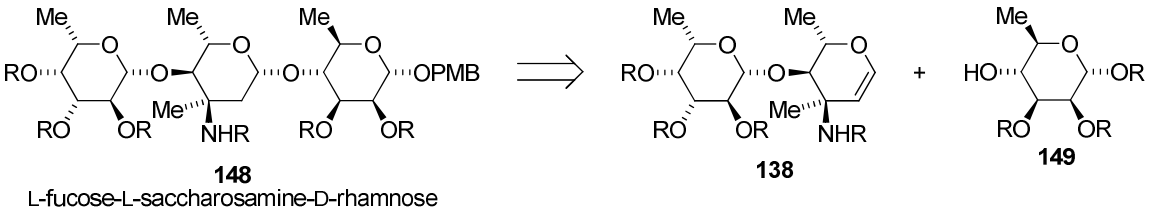
Scheme 1.19: Retrosynthetic Analysis of the L-Fucose-L-Saccharosamine-D-Digitoxose Target



Similar to the digitoxose analogue, rhamnose affixed trisaccharide **148** would be prepared (scheme 1.20). Glycosylation of rhamnoside **149** with glycal **138** would provide as second example of a Brønsted acid-promoted glycosylation. Unlike trisaccharide **136**, cycloisomerization of an alkyne alcohol would not be necessary. There is no degradation product from the saccharomicins to which **148** relates, though **148** is an important target

nonetheless, as it correlates to fuc-12 → sac-11 → rha-10 in saccharomicin A, and fuc-8 → sac-7 → rha-6 in both saccharomicin A and B.

Scheme 1.20: Retrosynthetic Analysis of the L-Fucose-L-Saccharosamine-D-Rhamnose Target



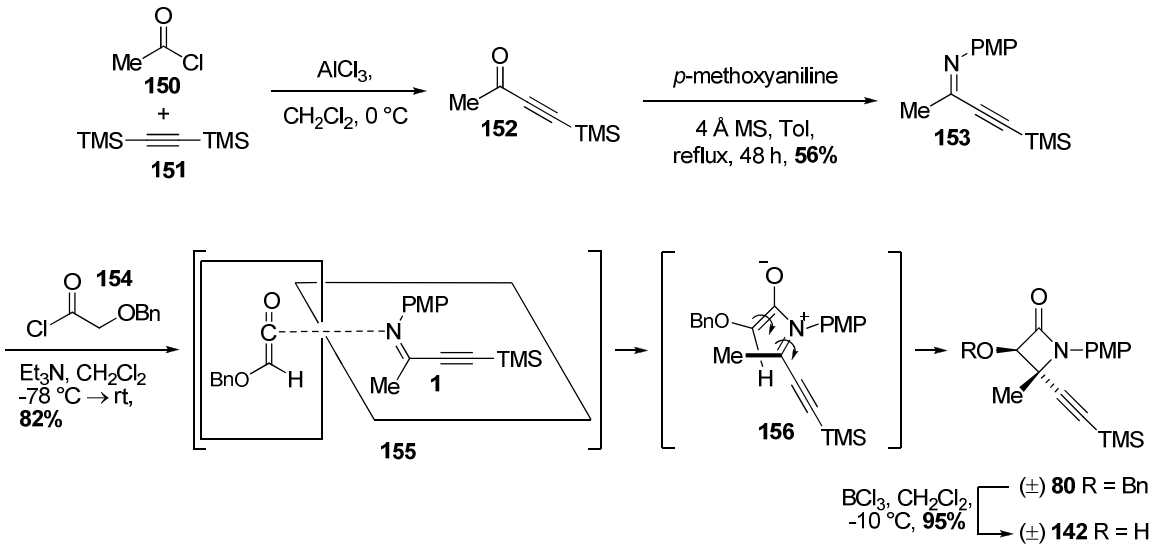
2. Results and Discussion

2.1. Synthesis of Peracetylated L-fucose-L-saccharosamine, Antipodal Degradation Product of Saccharomicin B

The synthesis began with the assembly of both trichloroimidate **50** and β-lactam **142**, in preparation for the Schmidt glycosylation. β-Lactam **142** was assembled first (scheme 2.1). Ketone **152** was synthesized from bis-(trimethylsilyl)acetylene and the acylium ion derived from acetyl chloride and aluminum chloride. After condensation of the ketone with *p*-methoxyaniline, a Staudinger cycloaddition[83] was carried out between imine **153** and benzyloxyacetyl chloride in the presence of triethylamine. The stereochemical outcome of the cycloaddition can be explained by a transition state in which the electron rich alkyne and benzyl ether repulse each other, leading to intermediate **156** in which these two functionalities are oriented away from one another. A conrotatory ring-closure then yields β-lactam **80**. The benzyl group was next

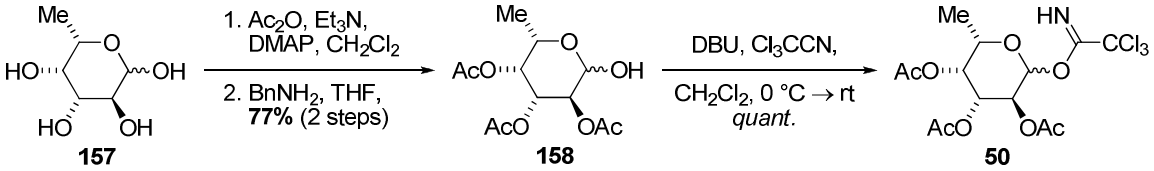
removed using boron trichloride to provide β-lactam **142**, ready as glycosyl acceptor.

Scheme 2.1: Synthesis of β-Lactam Glycosyl Acceptor **142**

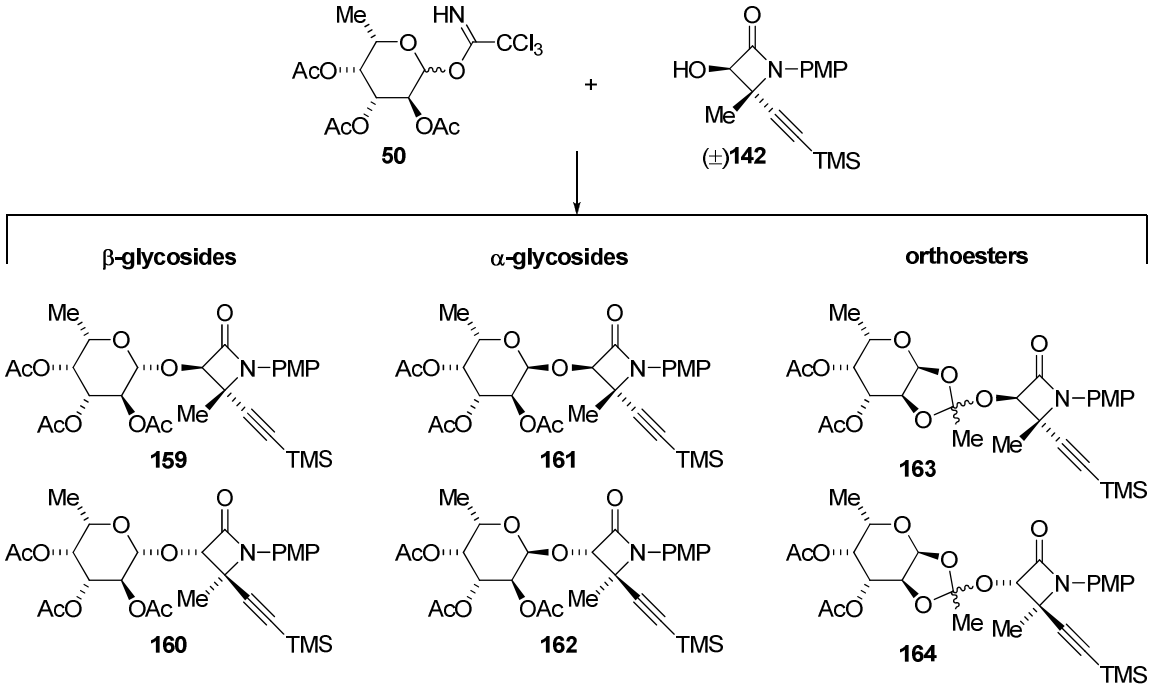


Fucosyl-donor **50** was prepared by a three-step functional group manipulation of L-fucose (scheme 2.2). Acetylation with acetic anhydride, followed by selective deprotection of the anomeric hydroxyl with benzylamine provided fucoside **158**. Trichloroimidate **50** was prepared by reaction of **158** with trichloroacetonitrile. Imidate **50** was always prepared immediately before use, though it could be stored without visible degradation (by ^{1}H NMR) for a few days. By allowing the reaction to equilibrate overnight (8 hours or more), the α-imidate could be prepared almost exclusively,[84,85] though the imidate α:β ratio did not seem to affect the stereochemical outcome of the subsequent Schmidt glycosylation.

Scheme 2.2: Synthesis of Trichloroimidate **50**



Scheme 2.3: Possible Schmidt Glycosylation Products

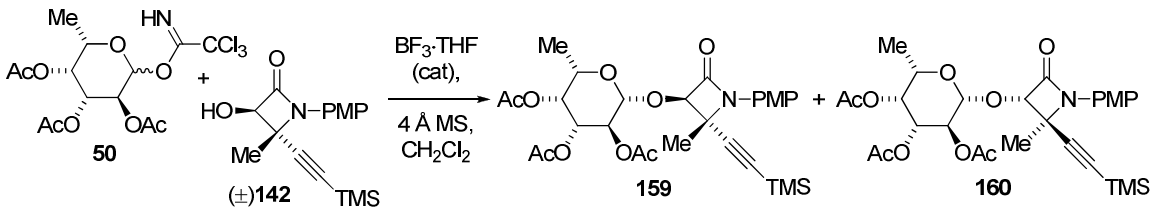


By carrying out the Schmidt glycosylation before opening of the β-lactam moiety, the fucose-saccharosamine congested linkage could be established earlier in the synthesis on a less complex and easily accessed acceptor. The racemic identity of **142** provided both the L,L- and L,D-motifs in one transformation. However, this glycosylation proved to be difficult. The distribution of possible products formed in the coupling is quite broad (scheme 2.3). Not only are the β- and α-glycosides available, but also the orthoesters which can exist as either of two diastereomers at the orthoester center. And

because the glycosyl acceptor is in this case racemic, the number of products doubles to eight distinct possible compounds, from which we aimed to select for only the β-glycosides **159** and **160**.

As we probed the reaction, several variables were tested. Nonpolar solvents were focused upon in order to encourage anchimeric assistance from the C2-acetate, though interchange between toluene and dichloromethane did not affect the yield or stereochemical outcome. Changes in concentration also did not greatly impact the reaction. It was temperature that proved to be by far the most influential reaction condition (table 2.1). Lower temperatures favored the orthoester formation (entries 1 and 2). Unfortunately, these compounds could not be purified unfortunately, as they were unstable and would decompose rapidly over time or with chromatography. Characteristic anomeric protons of the orthoesters could be seen by crude NMR at 6.30, 6.27, 6.08, and 5.99 ppm, along with extra methyl peaks near 1.6 ppm, indicating the orthoester methyls. As the temperature was increased, the orthoester products dropped off, and the β-glycosides took dominance. However, if warming was continued the reaction also produced α-adducts **161** and **162**. At temperatures above 0 ℃ the yield of the β-glycosides began to diminish from α-product formation, as well as hydration of the glycosyl donor. When the temperature was carefully maintained near -15 ℃, the β-glycosides **159** and **160** were produced reliably and in good yield. While the temperature sensitivity of the glycosylation necessarily limited scale, the reaction could be run in parallel and purified in one batch, which provided gram quantities of product as a mixture of the β-glycosides.

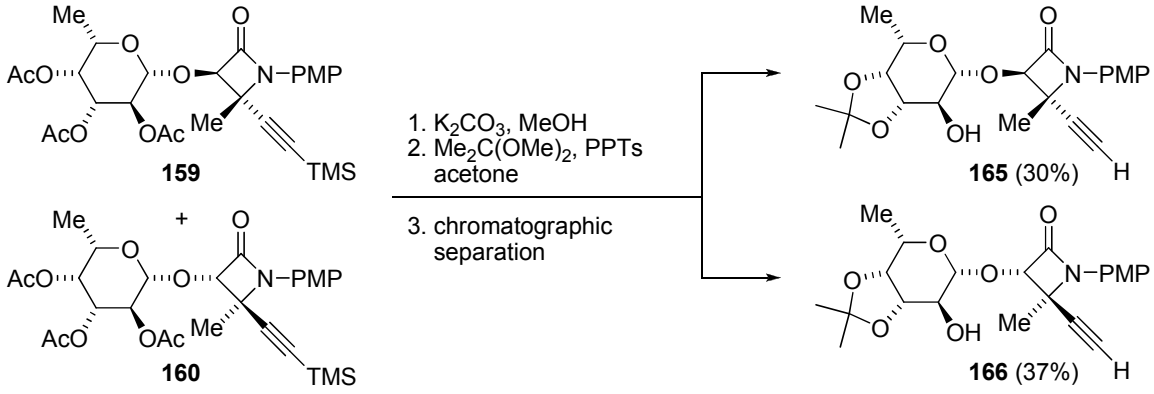
Table 2.1: Schmidt Glycosylation Conditions



entry	temperature (℃)	ratio of β-glycosides	ratio of α-glycosides	ratio of orthoesters[a]	%yield of 159 and 160
1	-78 ℃	1.0	-	12.2	7%
2	-45(± 5) ℃	1.0	0.2	1.5	45%
3	-25(± 5) ℃	1.0	0.2	0.9	48%
4	**-15(± 5) ℃**	**1.0**	**0.3**	**0.1**	**60–67%**
5	0 ℃	1.0	0.5	0.1	37%
6	rt	1.0	0.4	trace	17%

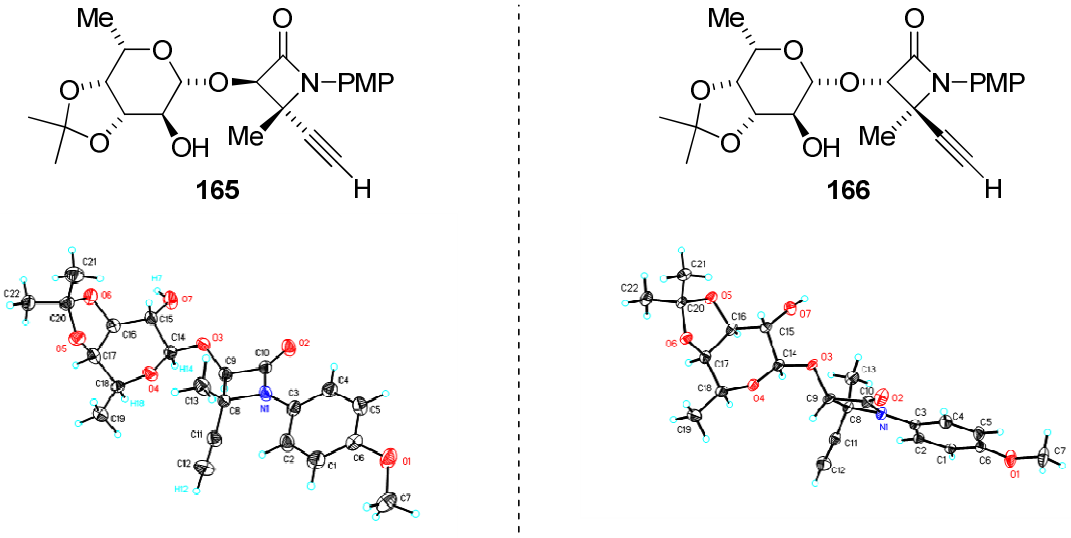
[a] The orthoester ratio is marked as the total of all orthoesters observed by crude ^{1}H NMR.

Scheme 2.4: Separation of β-Glycosides



Glycosides **159** and **160** were at first inseparable. Modifying the protecting group pattern around fucose soon provided analogues which could be resolved, and we prepared both compounds for ring-opening of the lactam moiety (scheme 2.4). Deacetylation under basic conditions, followed by acetonide formation across the C3,C4-hydroxyls of fucose afforded glycosides **165** and **166** independently. The absolute stereochemistry of the glycosides was firmly established by X-ray analysis (figure 14).

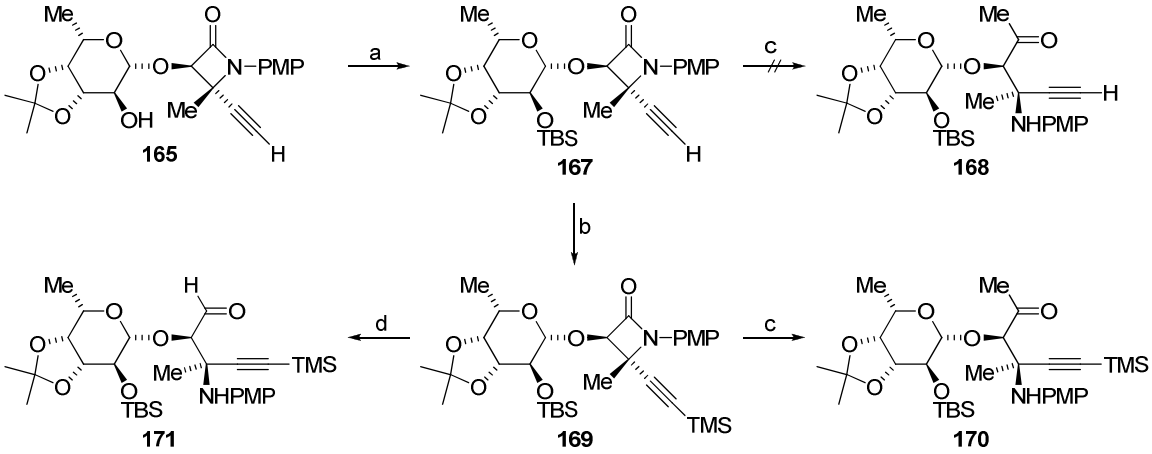
Figure 2.1: Glycosides **165** and **166** with Their Thermal Ellipsoid Diagrams



With a synthesis of both glycosides in hand, β-lactam **165** was carried forward. The stereochemistry of **165** would relate to L-saccharosamine once further functionalized, and the next major step in this process was to perform the ring-opening of the lactam moiety. To allow nucleophilic attack on the amide the acidic protons of both the C2-hydroxyl and the alkyne needed to be masked (scheme 2.5). The hydroxyl was protected as a TBS silyl ether (**167**), and the alkyne was blocked with a TMS group to provide compound **169**. From **169**, the

β-lactam could be opened using methyllithium to provide ketone **170**. No overalkylation was observed in the ring-opening process, despite methyllithium being used in excess. The ketone is likely safeguarded in this way due to the electron rich *p*-methoxyphenyl substituted nitrogen. A stable hemiaminal chelate is probably formed with lithium *in situ*, and does not collapse until the reaction is quenched. In this way ketone **170** could be produced in nearly quantitative yield.

Scheme 2.5: Ring-Opening of β-Lactam



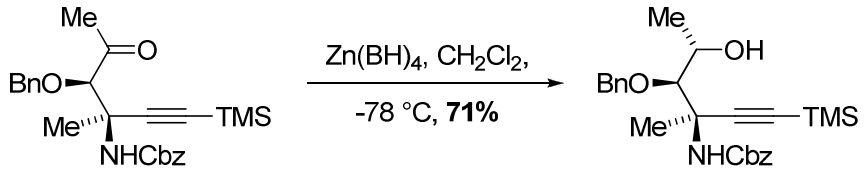
(a) TBSCl, imidazole, DMF, **98%**. (b) MeLi, THF, -78 °C, *then* TMSCl, **87%**. (c) MeLi, THF, -78 °C, **97%**. (d) DIBAL, CH_2Cl_2, -78 °C, **99%**.

Ring-opening without installation of the alkynyl-TMS to furnish **168** could not be accomplished. Presumably the alkyne undergoes deprotonation, and the resulting alkynyllithium species possesses enough Coulombic repulsion to prevent a second equivalent of methyllithium from attacking the carbonyl. At -78 °C no net reaction was observed, or a complex mixture was formed if the reaction was allowed to warm. Alternatively, a one pot procedure can be envisioned in which the alkyne is deprotonated with methyllithium, quenched with

TMSCl, then ring-opened by adding more methyllithium. This protocol was indeed tried, but the yield of ketone **170** was eroded to 77%. As an alternative to **170**, the lactam could instead be opened using diisobutylaluminum hydride (DIBAL) to produce aldehyde **171**, also in excellent yield.

The next transformation involved setting the C5-stereochemistry of saccharosamine to (*S*)-diastereomer, a process that would emerge as a significant challenge. During our groups synthesis of a racemic saccharosamine glycal monomer, the C5-position was set under chelating conditions using zinc borohydride in dichloromethane (Scheme 2.6).[57] While chelation worked well for the monomer **172**, the system presented by glycosidic ketone **173** made predicting the stereochemical outcome from asymmetric induction more difficult (Scheme 2.7). Felkin-Ahn control, where the electron withdrawing glycosidic bond behaves at the large group through antiperiplanar stabilization (**A**), might be expected to provide the (*R*)-diastereomer. It is not clear that this would be the case however, as the quaternary center could instead dominate as the larger substituent.

Scheme 2.6: A Substantial Difference in Reductions

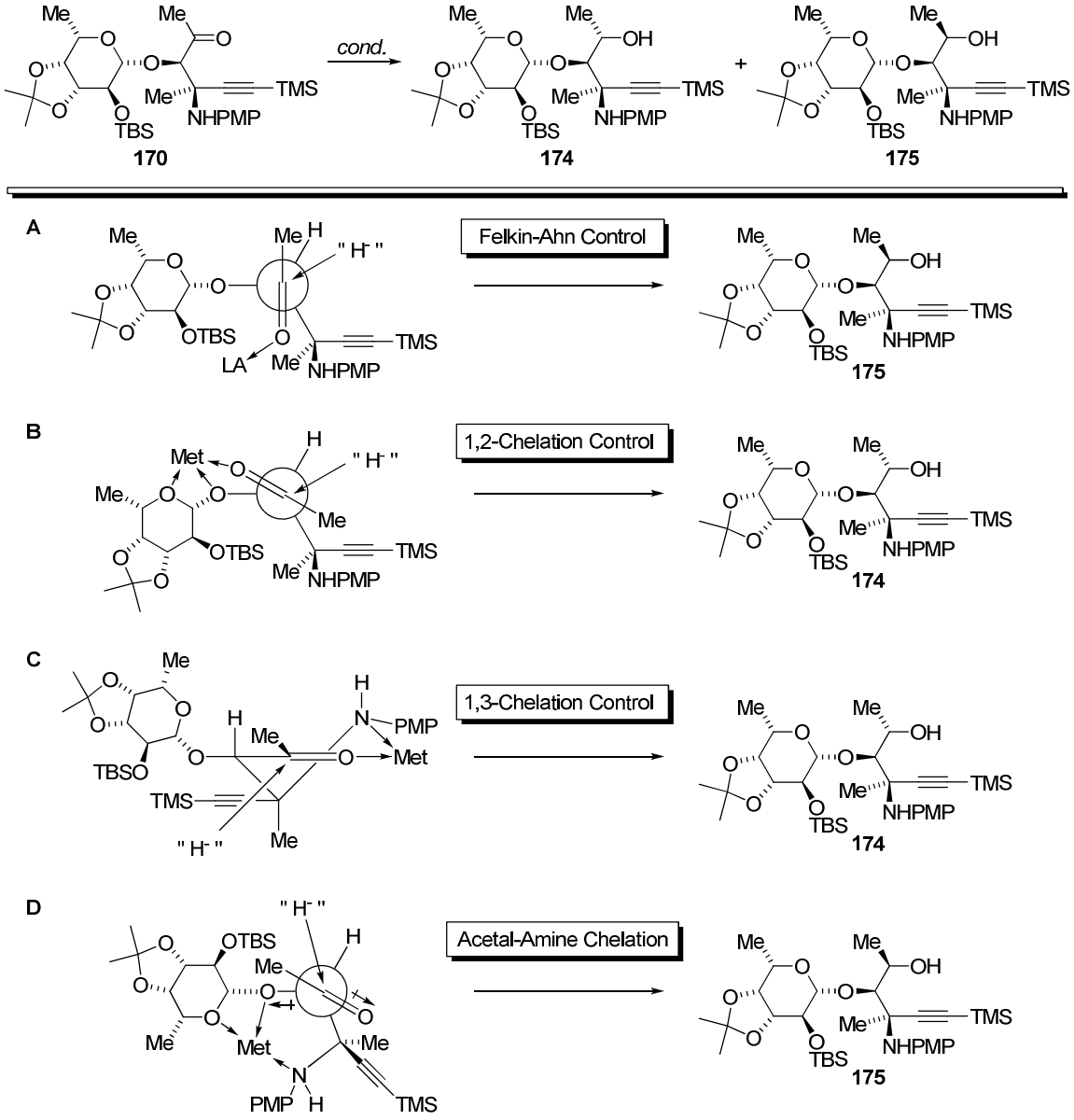


172 **173**

A concrete chelation control model was more difficult still to predict. The acetal moiety inherent to the glycosidic bond was certainly capable of coordination to a Lewis acidic species. Use of a glycosyl linkage for chelation

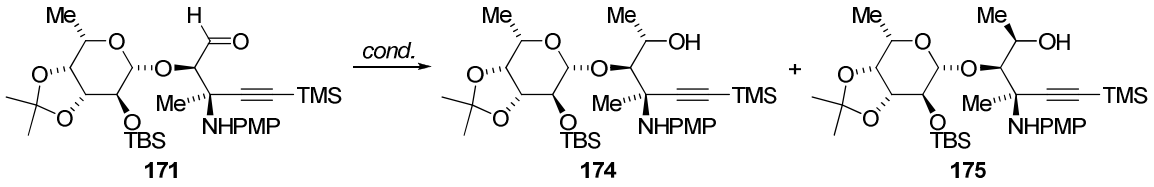
control remains unprecedented in the literature and multiple models can be reasoned. One possibility is that the linkage would behave akin to a methoxymethyl ether (**B**), leading to the desired (*S*)-diastereomer. It is likely however that the conformation of the pyranoside would impact its behavior as a chelating agent in undetermined ways.

Scheme 2.7: Potential Asymmetric Induction Models for Ketone **170**



The situation was complicated further by the presence of the electron rich, *p*-methoxyphenyl-protected amine. Exchanging the PMP group with acetamide or carbamate sufficiently increased the acidity of the C4-saccharosaminyl hydroxyl so that epimerization became problematic. For stability the PMP group was left intact, opening up more possible chelation conformations such as **C** and **D**. Despite the complexity of ketone **170** over our previous examples, we were interested to see if substrate control could indeed be used to set the C5-stereocenter selectively. Fortunately, access to both aldehyde **171** and ketone **170** meant we could either utilize alkylation or reduction respectively to establish the secondary alcohol **174**.

Table 2.2: Methylation of Aldehyde **171**



171 **174** **175**

entry	conditions	recovered **171**	% **174**	% **175**
1	MeLi, THF, -78 °C	-	10%	-
2	$MeCeCl_2$, THF, -78 °C → 20 °C	complex mixture		
3	Me_2CuLi, THF, -78 °C → 20 °C	complex mixture		
4	$Me_2CuMgBr$, THF, -78 °C	complex mixture		

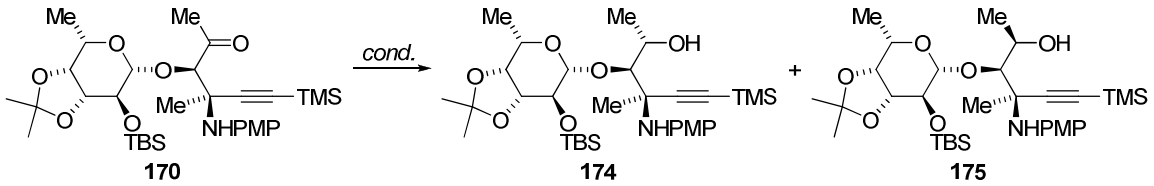
Alkylation of aldehyde **171** was attempted first as Felkin-Ahn conditions would be expected to provide the desired (*S*) diastereomer (table 2.2). Unfortunately, the aldehyde was prone to epimerization of the α-carbon (observed by crude NMR), and a complex mixture was formed under most conditions. The earliest attempt using methyllithium did produce the desired secondary alcohol **174**, but only in a sparse 10% (entry 1). Using a softer nucleophile such as methylcerium[86,87] failed to improve the situation, being unreactive at lower temperatures, and producing only a complex mixture when warmed gradually (entry 2). Comparatively mild organocopper species gave similar results to methylcerium.[88,89] With no successful alkylations of **171**, we instead turned to the reduction of ketone **170**. We reasoned that the higher pKa of **170** would make it more amenable to nucleophilic attack over enolate formation.

Luche reduction of ketone **170** proceeded with excellent selectivity towards the Felkin-Ahn product, providing the undesired (*R*)-diastereomer **175** (table 2.3, entry 1). Attempts to invert the stereochemistry of alcohol **175**, by a Mitsunobu reaction[43] failed. Using either acetic or benzoic acid, DEAD only returned starting material, and switching to DIAD again resulted in recovered starting material, this time with a small amount of degradation observed.[90,91]

Chelating conditions were next attempted and the same conditions used on monomer **172** (zinc borohydride in dichloromethane) were tried first (entry 2). The conditions proved to be highly irreproducible however, due to the insolubility of zinc borohydride in dichloromethane. To circumvent this problem, titanium

tetraethoxide was added to the reaction mixture and allowed time to form a stable chelate before the reducing agent was introduced (entry 3).[92] While this pre-chelation technique did allow the reduction to be carried out with reproducible

Table 2.3: Selective Reduction of Ketone **170**



170 **174** **175**

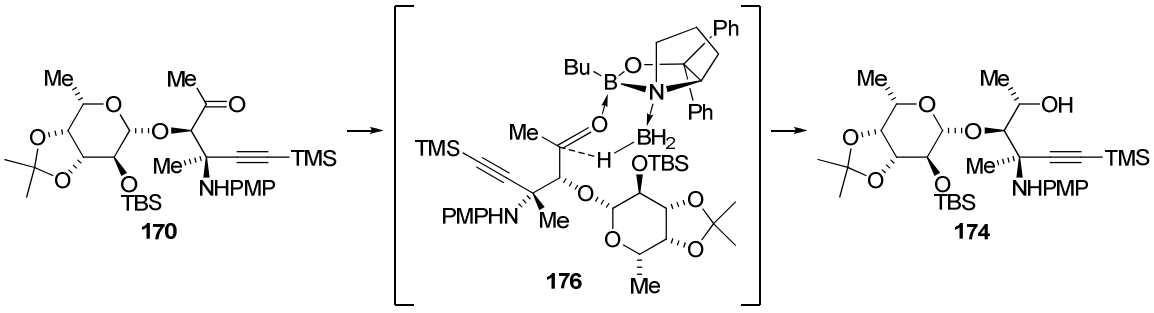
entry	Conditions	recovered **170**	% **174**	% **175**
1	$NaBH_4$, $CeCl_3$, CH_2Cl_2, MeOH, -78 °C → rt	-	-	91%
2	$Zn(BH_4)_2$, CH_2Cl_2, -78 °C → 0 °C	irreproducible		
3	$Zn(BH_4)_2$, $Ti(OEt)_4$, CH_2Cl_2, -50 °C → 0 °C	-	38%	33%
4	$BH_3{\cdot}SMe_2$, $Ti(OEt)_4$, CH_2Cl_2, -78 °C → -60 °C	34%	26%	22%
5	$NaBH_4$, 15-crown-7, $Ti(OEt)_4$,CH_2Cl_2, -78 °C → 0 °C	48%	14%	36%
6	DIBAL, CH_2Cl_2, -78 °C	-	-	95%
7	LAH, THF, -78 °C	-	20%	73%
8	LAH, $Ti(OEt)_4$, CH_2Cl_2, -78 °C	-	-	76%
9	(*R*)-Me-CBS (50 mol%), $BH_3{\cdot}THF$, THF, 0 °C	9%	62%	16%
10	**(*R*)-Bu-CBS (65 mol%), $BH_3{\cdot}THF$,THF, -78 °C → -5 °C**	**-**	**81%**	**~5%[a]**

[a] The minor diastereomer contained small amounts of impurity from the CBS catalyst.

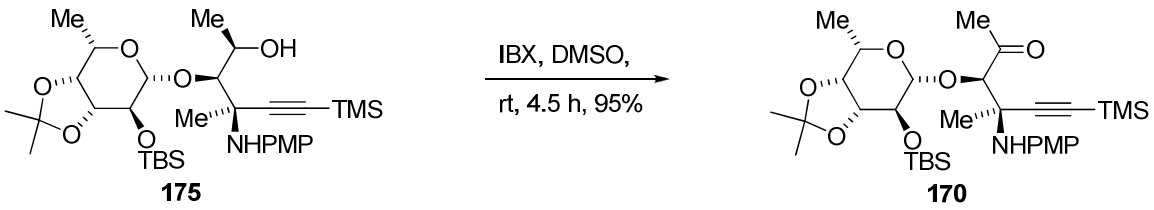
results, selectivity of the transformation was still low. Switching reducing agents to borane-dimethyl sulfide complex or sodium borohydride likewise did not improve selectivity or access useful amounts of alcohol **174** (entries 4 and 5). Reductions using aluminum-based reagents were also attempted. The free coordination site on aluminum might interact in such a way as to exert a meaningful degree of stereocontrol. We soon found that selectivity was indeed high for these reductions, but unfortunately both diisobutylaluminum hydride and lithium aluminum hydride favored the Felkin-Ahn product **175**. As our attempts to invert the stereochemistry of this center failed, these reductions were also unproductive.

Our attention next turned to asymmetric protocols, and the desired (*S*)-diastereomer **174** was at last produced as the major product when a Corey-Bakshi-Shibata reduction was employed.[93,94] The methyl CBS-catalyst gave the first truly favorable results, affording the (*S*)-diastereomer in 62% with a 4:1, *S* : *R* ratio. By switching to the butyl CBS analogue, and a slightly higher catalytic loading, the yield was improved to 81% of the (*S*)-diastereomer, and a 15:1, *S* : *R* ratio. Substituting borane tetrahydrofuran complex for catecholborane slowed the rate of reaction, but did not improve the selectivity or yield. The selectivity can be explained by the postulated model **176**, in which the methyl group of the ketone is the smaller substituent of the ketone, and the rest of the glycoside is extended away from the catalyst-ketone complex (scheme 2.8). It is also worth noting that the minor diastereomer could be recycled back to ketone **170** using an IBX oxidation (scheme 2.9.)

Scheme 2.8: Postulated Model for the CBS Reduction of Ketone **170**

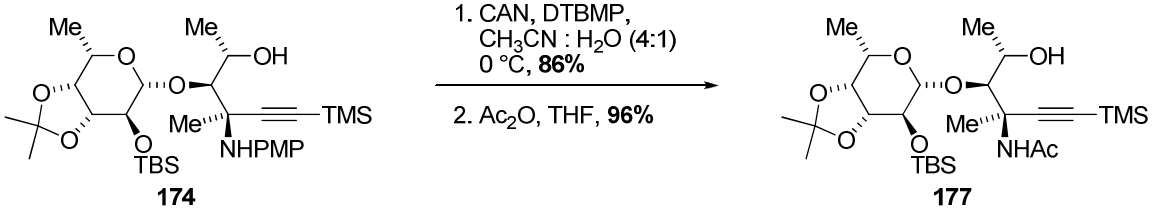


Scheme 2.9: Recycling Alcohol **175** By IBX Oxidation

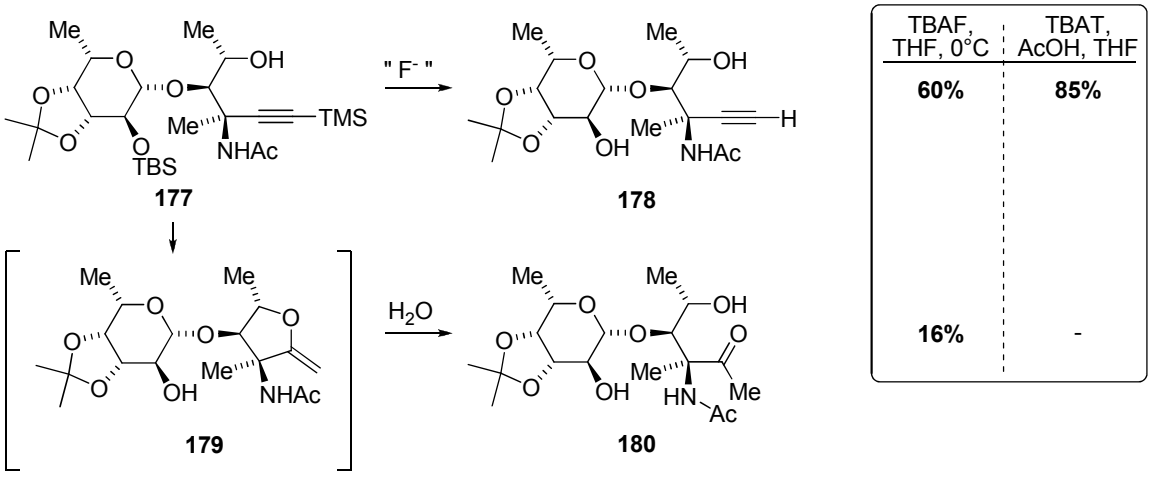


With a robust synthesis of secondary alcohol **174** in hand, the *p*-methoxyphenyl group needed to be removed before cycloisomerization was performed (scheme 2.10). Oxidative cleavage using ceric ammonium nitrate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as a proton sponge, cleanly removed the aromatic ring. The amine was then protected as acetamide **177** using acetic anhydride in the absence of external base. When the protection was conducted at 0 ℃, significant amounts of acetate ester accumulated. Presumably steric encumbrance around the amine slowed acetamide formation, and the amine was itself sufficiently basic to promote the ester product. By running the reaction at ambient temperature, and using acetic anhydride only in small excess, acetylation of the hydroxyls could be avoided.

Scheme 2.10: Replacing PMP with Acetamide



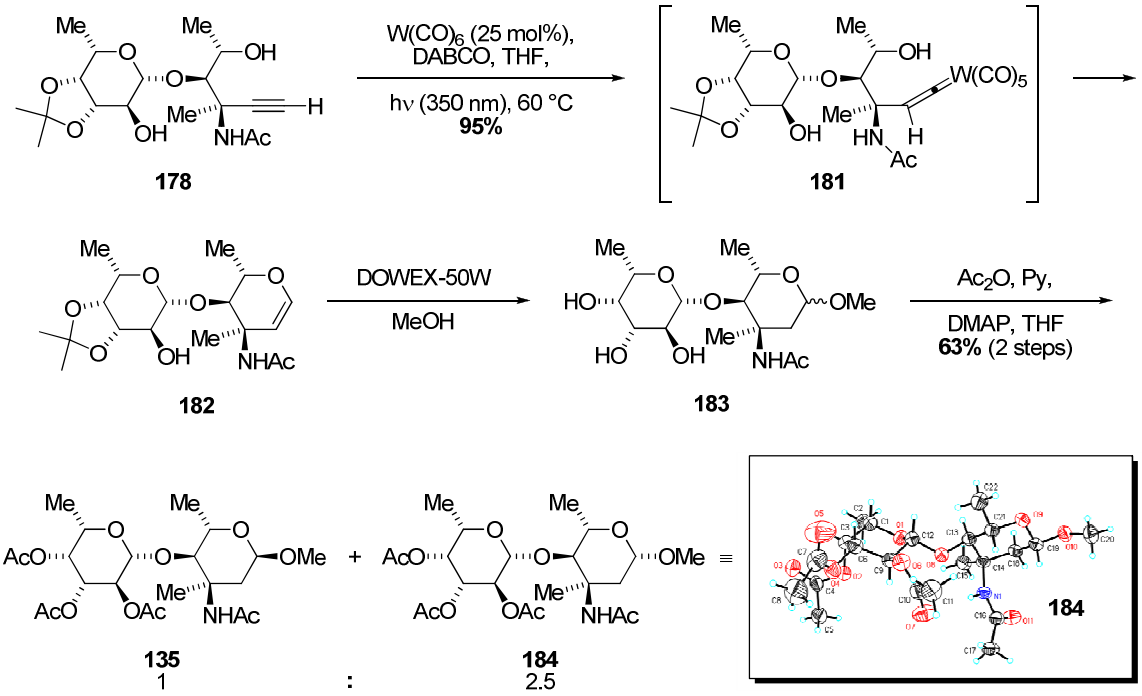
Scheme 2.11: Desilylation of Alkyne Alcohol **177**



Desilylation of both the TBS ether and alkynyl TMS using TBAF was then performed to reveal key alkyne alcohol **178** (scheme 2.11). Surprisingly, a significant amount of material was diverted to ketone **180** during this process. Hydration of an alkyne alcohol under basic conditions is not unprecedented, though more strongly basic conditions are typically employed.[95-97] It is likely that the quaternary center accelerates the hydration due to the Thorpe-Ingold effect. Buffering with acetic acid prevented ketone formation at shorter reaction times (8 h), but also greatly slowed removal of the silyl ether. If the reaction times were extended, ketone **180** was again observed. By switching to tetrabutylammonium

difluorotriphenylsilicate,[98,99] which is a far more hydrophobic fluoride source, and again buffering with acetic acid, ketone **180** could be avoided completely.

Scheme 2.12. Cycloisomerization and Final Functional Group Manipulations of Antipodal-Degradation Product, L-Fucose-L-Saccharosamine



Conversion of alkyne alcohol **178** to saccharosamine glycal **182** was next accomplished by our tungsten-catalyzed cycloisomerization method (scheme 2.12). Pleasingly, the isomerization proceeded in excellent yield, with no exo-cyclization visible in the crude reaction mixture. Glycal **182** was then exposed to DOWEX-50W acid resin in methanol, which removed the fucosyl acetonide and converted the glycal to methyl glycosides **183**. Acetylation of the hydroxyls then provided the L-fucose-L-saccharosamine degradation product **135**, along with related β-anomer **184** in 63% over two steps and a 2.5:1, β : α ratio. After contacting the authors of the original saccharomicin paper, they kindly provided us the characterization data of **133** for comparison. The α-anomer **135** was

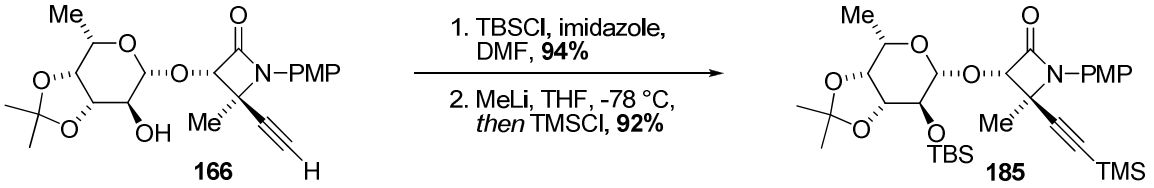
found to match the D-fucose-D-saccharosamine degradation product by ^{1}H and ^{13}C NMR. An X-ray crystal structure was obtained of **184**, further confirming the disaccharide structure.

2.2. Synthesis of peracetylated L-fucose-D-saccharosamine disaccharide

At the outset of our synthetic work we could make an educated decision to use L-fucose due to its natural abundance. However, our choice for saccharosamine was blind as the saccharomicins have been the only reported occurrence of this pyranoside and thus we did not know which enantiomer would be more common. No characterization data relating to the fucose-saccharosamine disaccharide degradation product **133** had been reported, and we could not be sure what materials would eventually become available for comparison. We sought then to take advantage of the racemic nature of β-lactam **142** to access both the L,L- and the L,D-diastereomers of the degradation product. Access to both disaccharides would provide a powerful point of comparison in determining the relative stereochemistry of degradation product **133**. The syntheses could be carried out in tandem, and ideally would involve very similar chemistry.

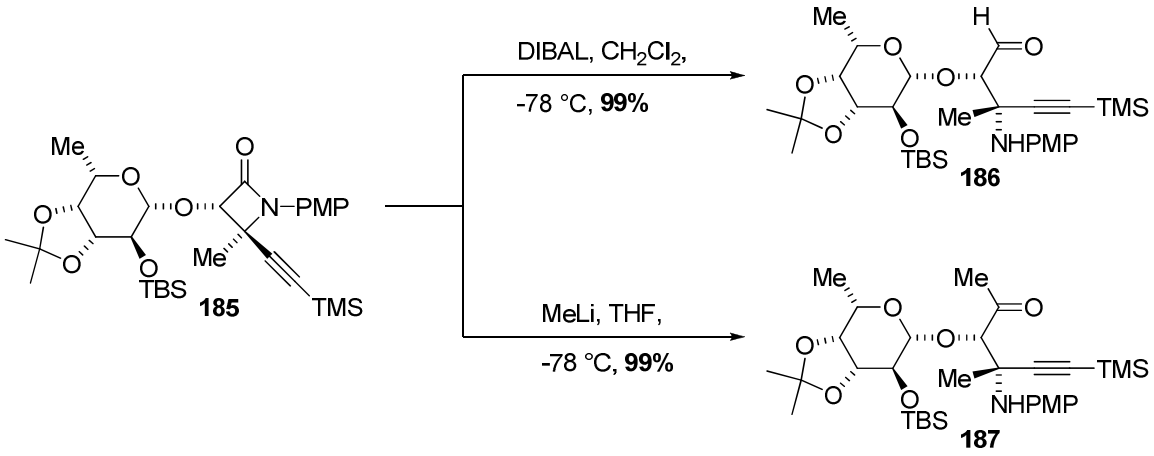
As with the L-fucose-L-saccharosamine synthesis, the acidic protons on glycoside **166** needed to be masked before ring-opening (scheme 2.13). The fucosyl C2-hydroxyl was protected as a silyl ether, and the alkyne blocked with a TMS group. Both of these steps occurred in excellent yield.

Scheme 2.13: Masking Acidic Protons



Ring-opening of the β-lactam was then carried out (scheme 2.14). Aldehyde **186** could be formed in nearly quantitative yield using DIBAL, or ketone **187** produced with MeLi, again with nearly quantitative conversion. The next step then involved setting the C5-stereocenter of D-saccharosamine, but this proved to be just as difficult as for the L,L-analogue.

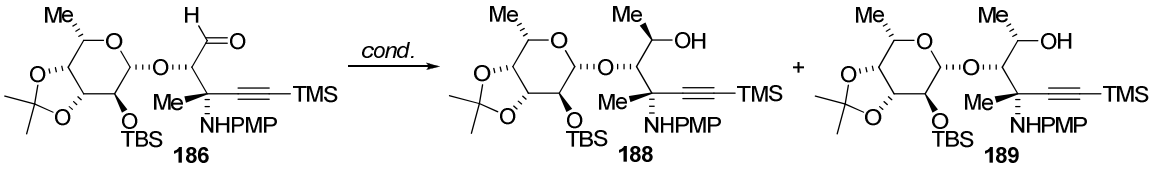
Scheme 2.14: Ring-opening of β-lactam **185**



Several conditions were attempted for the alkylation of aldehyde **186** (table 2.4). As with related aldehyde **171**, the acidity of the α-proton was problematic, and epimerization occurred under a variety of alkylating conditions, especially when run at temperatures ≥ 0 °C. Addition of methyllithium at -78 °C did favor the desired (*R*)-diastereomer, although in modest yield even after optimization (entry 1). The addition of hexamethylphosphoramide inverted the

selectivity, and instead favored secondary alcohol **193** (entry 2). Other methylation conditions were tried including methylcerium and methylcuprate reagents, but these conditions were unreactive at low temperatures and formed complex mixtures upon warming. Despite its basicity, the methyl Grignard reagent was also tried, although it too led to a complex mixture.

Table 2.4: Methylation of Aldehyde **186**

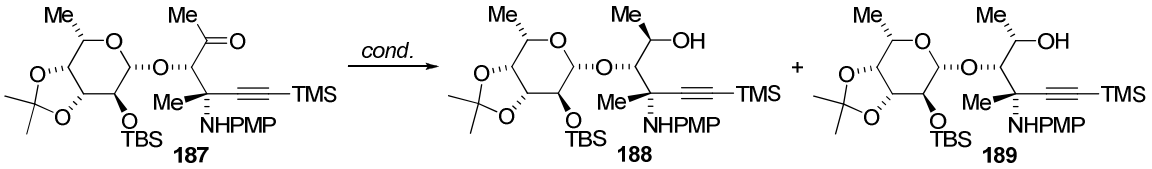


entry	conditions	recovered **186**	% **188**	% **189**
1	MeLi, Et_2O, -78 °C	-	41%	12%
2	MeLi, HMPA, Et_2O, -78 °C	-	11%	39%
3	MeMgBr, THF, 0 °C	complex mixture		

Inversion of the step order by reducing ketone **187** was more successful that the alkylation of related aldehyde. Luche reduction conditions again provided undesired Felkin-Ahn product **189**, which could not be inverted using a Mitsunobu protocol (table 2.5). Whereas chelation-controlled reduction conditions had failed and asymmetric CBS reduction succeeded for ketone **170**, the reverse was true for ketone **187**. Use of (*S*)-methyl-CBS catalyst with borane did not provide a high degree of selectivity, and actually slightly favored alcohol **189**. Switching to the *n*-butyl CBS catalyst did not improve the selectivity.

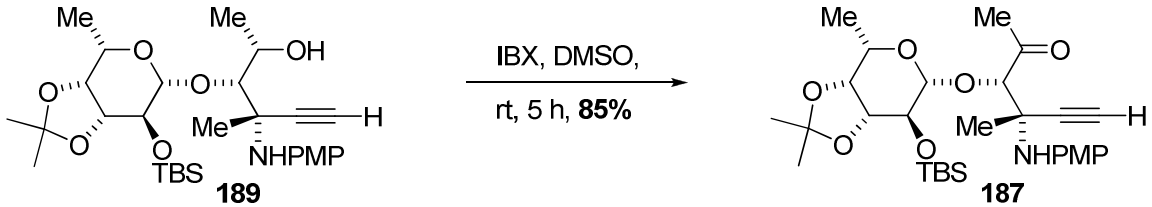
Instead, chelation-controlled reduction provided the best results. Prechelation using titanium ethoxide and reduction with zinc borohydride provided the desired secondary alcohol **188** in useful amounts. Because the yield of **188** was not particularly high, it was especially important that the minor diastereomer could be efficiently oxidized back to ketone **187** using IBX (scheme 2.15).

Table 2.5: Reduction of Ketone **187**



entry	conditions	recovered **187**	% **188**	% **189**
1	$CeCl_3$, $NaBH_4$, CH_2Cl_2 : MeOH (5:1)	-	-	81%
2	(*S*)-Me-CBS (50 mol%), BH_3·THF, THF, 0 °C	22%	30%	43%
3	$Zn(BH_4)_2$, $Ti(OEt)_4$, CH_2Cl_2, -50 °C	-	51%	15%

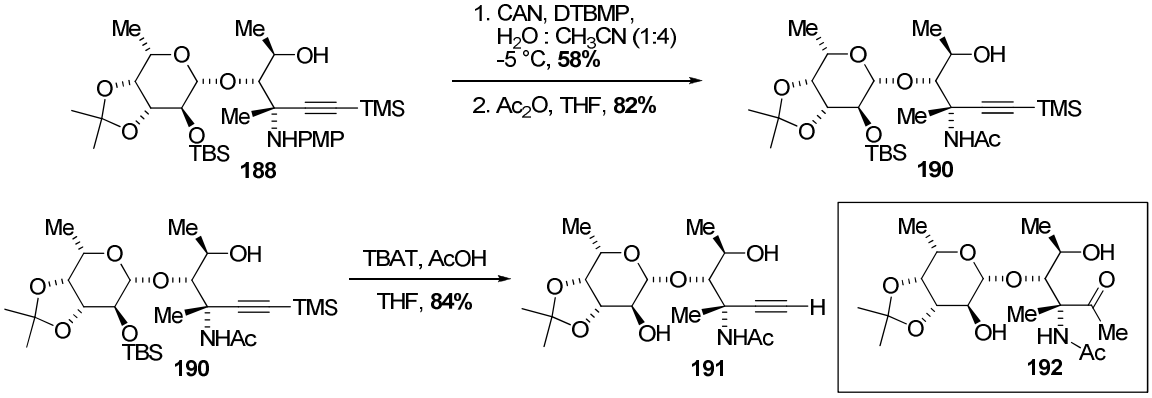
Scheme 2.15: Oxidation of Secondary Alcohol **189**



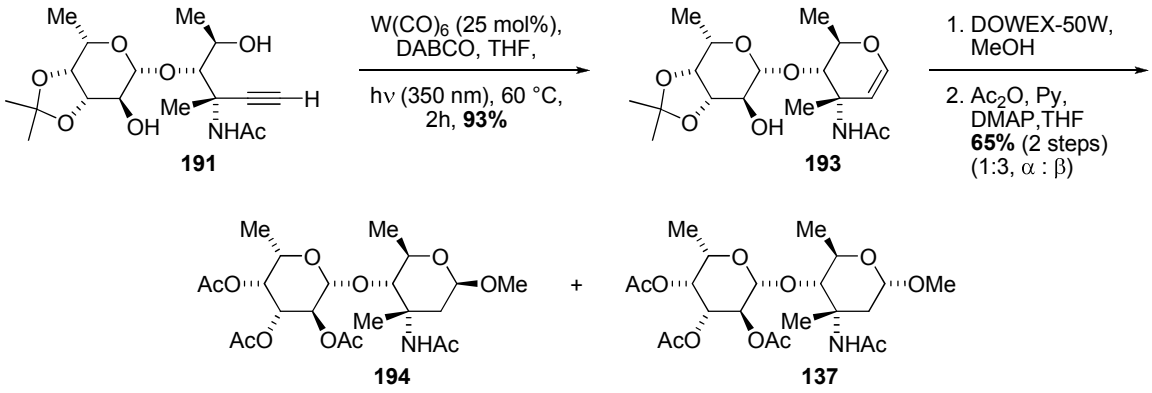
With all of the key stereocenters set, protecting group manipulation in preparation for ring-closure was carried out (scheme 2.16). The *p*-methoxyphenyl group was oxidatively cleaved using ceric ammonium nitrate, though in comparatively low yield compared to alcohol **174**. Acetamide was

selectively installed, with careful control to avoid acetylation of the hydroxyls. The best results for desilylation were provided by tetrabutylammonium difluorotriphenylsilicate. As observed before, the alkyne functionality was prone to hydration when a more basic form of fluoride was used, even when buffered by acetic acid.

Scheme 2.16: Conversion to Alkyne Alcohol **191**



Scheme 2.17: Cycloisomerization and Final Functionalization of Peracetylated L-Fucose-D-Saccharosamine Methyl Glycosides



Tungsten-catalyzed cycloisomerization was then carried out in excellent yield, with no exo-product visible in the reaction (scheme 2.17). Acetonide deprotection and concomitant methyl glycoside formation was next conducted

with DOWEX-50W resin in methanol. Acetylation of the hydroxyls then afforded the target L-fucose-D-saccharosamine disaccharide as a mixture of both the α- and β-methyl glycosides **137** and **194**. The anomers were difficult to separate, and ultimately only **194** could be characterized as a single diastereomer. Despite the mixture, all of the peaks relating to each anomer could be clearly assigned. When compared to degradation product **133** it was clear that neither of the L,D-diastereomers matched, and thus this firmly confirmed the relative stereochemistry of **133**.

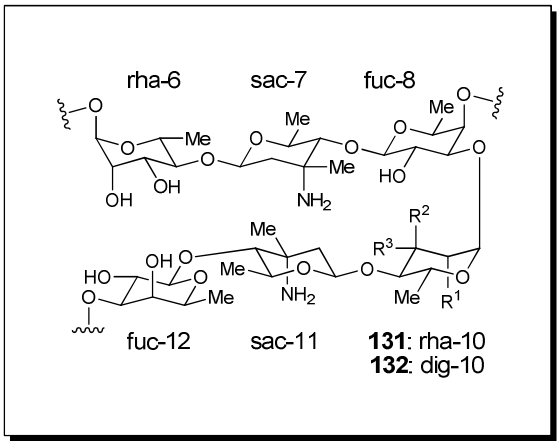
2.3. Synthesis of L-fucose-L-saccharosamine-D-digitoxose and L-fucose-L-saccharosamine-D-rhamnose

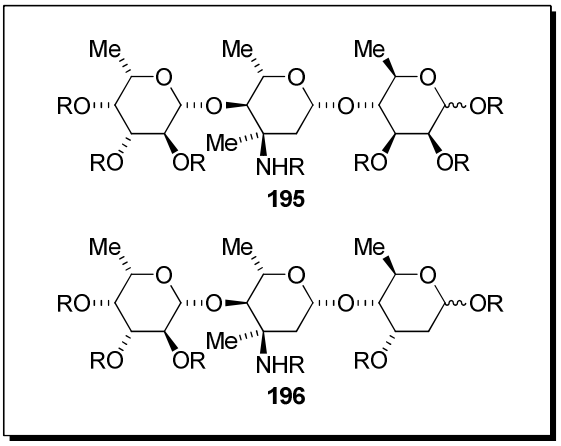
With a disaccharide synthesis well in hand, we next turned our attention to the synthesis of two key trisaccharides, L-fucose-L-saccharosamine-D-rhamnose **195** and L-fucose-L-saccharosamine-D-digitoxose **196** (figure 2.2). The rhamnosyl-trisaccharide would represent sugars 12-11-10 in saccharomicin A, and 8-7-6 in both saccharomicin A and B. Similarly the digitoxose-affixed trisaccharide would relate to sugars 12-11-10 in saccharomicin B. Synthesis of these trisaccharides would provide larger building blocks for the synthesis of the core regions of the natural products. It was important then, that as these compounds were brought forward, they pass through states in which the trisaccharides might be used as either glycosyl donors or glycosyl acceptors.

We envisioned constructing these trisaccharides by a Brønsted acid-promoted glycosylation between a saccharosaminyl glycal and an appropriate

glycosyl acceptor relating to either rhamnose or digitoxose (scheme 2.18). The efficiency of such a linkage was attractive, as we could use a glycal modified from, or closely related to, our previously synthesized saccharosaminyl glycal **182**. Our group has had success with protic acid-catalyzed glycosylations of glycals,[62,79] and we were interested to test the method on the saccharosamine motif. However, the success of such a glycosylation was not guaranteed, and thus we were keen to try a test case both for efficacy and stereoselectivity.

Figure 2.2: Trisaccharide Targets from the Core Regions of Saccharomicin A and B

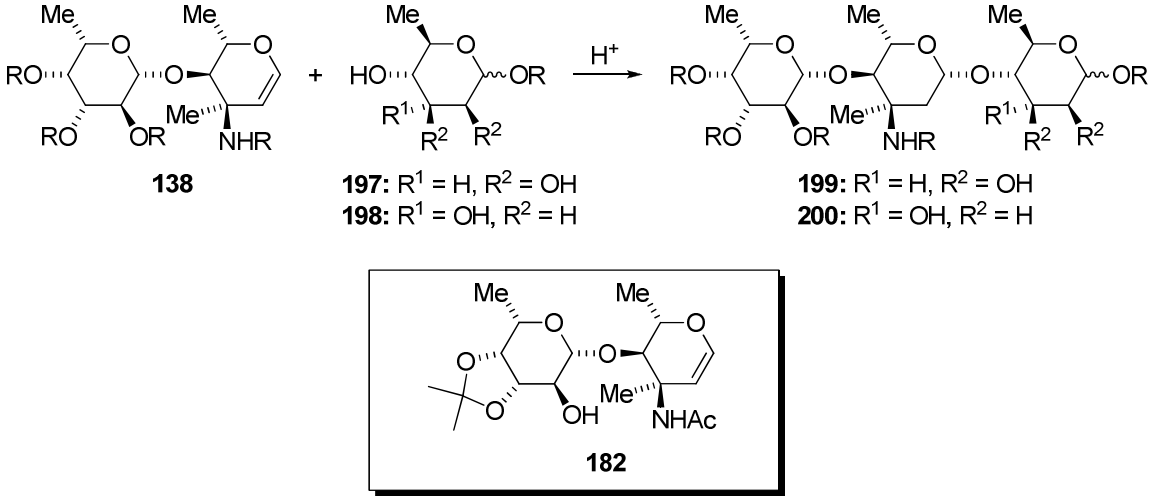




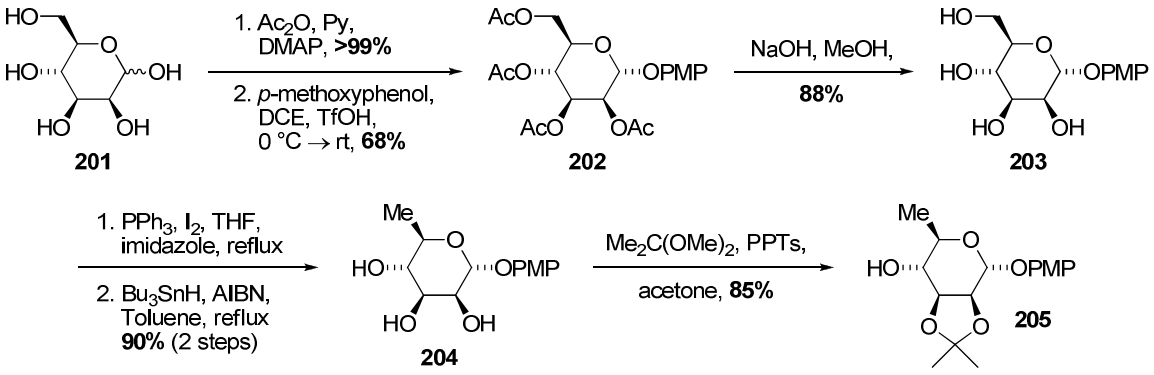
In order to try out the acid-promoted glycosylation, we required an appropriate glycosyl acceptor. As neither D-rhamnose nor D-digitoxose is commercially available, any pyranoside acceptor we wished to use had to be synthesized. The known D-rhamnose analogue **205** was easily and quickly accessed for this purpose (scheme 2.19).[100] From D-mannose acetylation then exchange of the C1-acetate with *p*-methoxyphenol provided aryl glycoside **202** exclusively as the α-anomer. Saponification of the remaining esters was then

followed by a two-step reduction procedure. The primary C6-hydroxyl was displaced by iodide, then reductively cleaved using tributyltin hydride to reveal rhamnoside **204**. The C2- and C3-hydroxyls were then protected as acetonide, leaving the C4-hydroxyl available for glycosylation.

Scheme 2.18: Hypothesized Brønsted Acid-Catalyzed Glycosylations



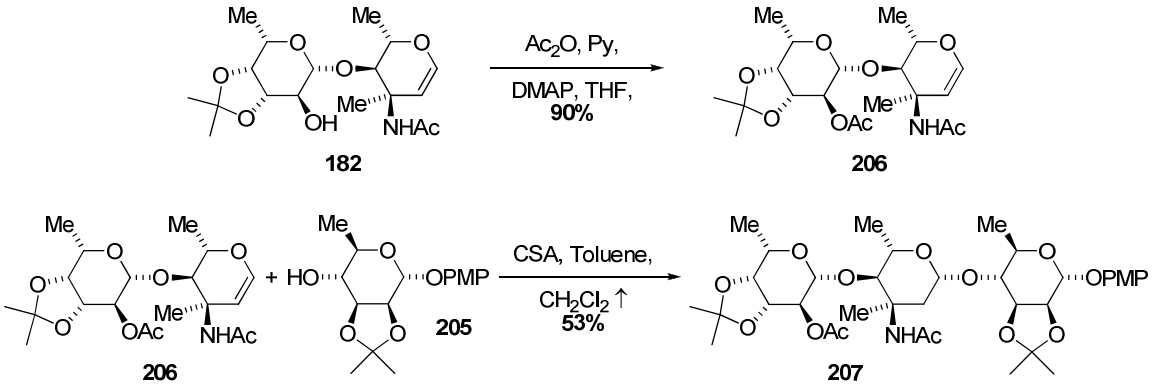
Scheme 2.19: Preparation of D-Rhamnose Glycosyl Acceptor **205**



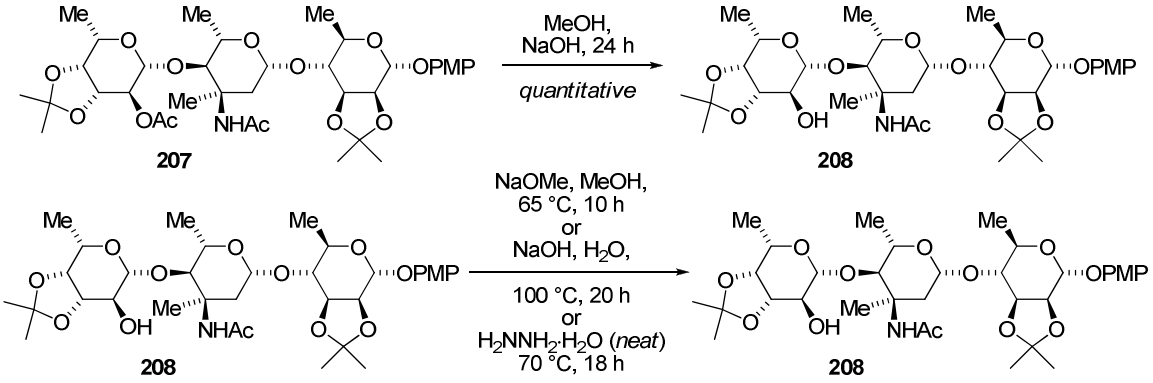
For the glycosyl donor the C2-hydroxyl of glycal **182** was masked as acetate to avoid competition during the glycosylation. With both coupling partners in hand, the Brønsted acid-promoted glycosylation was carried out using (+)-camphor-10-sulfonic acid (scheme 2.20). Pleasingly, the L-fucose-L-

saccharosamine-D-rhamnose trisaccharide **207** was produced, yielding the desired β-glycoside in 53%. The α-anomer could not be identified in the reaction, though this may have been due to scale. The results were encouraging overall, and though optimization would be required, glycoside **207** demonstrated that the Brønsted acid methodology indeed worked.

Scheme 2.20: Testing the Brønsted Acid-Promoted Glycosylation



Scheme 2.21: A Robust Acetamide Protecting Group

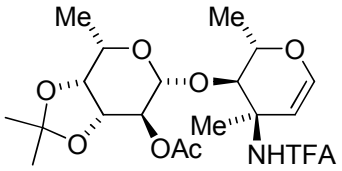


Trisaccharide **207** also presented a good opportunity to test the deprotection of the saccharosaminyl C3-acetamide (scheme 2.21). Attempts at deprotection under basic conditions soon proved how robust was the hindered amide. Sodium hydroxide in methanol smoothly removed the fucosyl acetate,

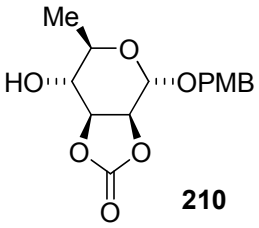
but the acetamide remained completely intact. Freshly prepared sodium methoxide in refluxing methanol or a 1 M solution of aqueous sodium hydroxide at 100 ℃ both failed, as did neat hydrazine monohydrate.

The model system glycosylation had provided several important pieces of information. The Brønsted acid-promoted glycosylation did indeed work, although the reaction would require some optimization. We also determined that a more labile nitrogen protecting group would be required. What remained then was to synthesize a disaccharide with an amine protecting group that could be removed from late stage oligosaccharides. In addition the functional group pattern of digitoxose and rhamnose monomers functionalization would also need to be finalized (figure 2.3). Thus we chose to protect the amine as trifluoroacetamide **209** which should be easier to deprotect, ideally under the same conditions as the fucosyl C2-acetate. For the rhamnose monomer, we desired that the C3,C4-hydroxyls could also be deprotected under similar conditions to the acetate and trifluoroacetamide, and so we decided upon a carbamate. The reducing end of rhamnose would best be served by a moiety which could be removed under conditions orthogonal to both the carbonyl functional groups and the fucosyl acetonide. Such an arrangement optimally would provide a trisaccharide which could be converted to either a glycosyl donor or acceptor. The digitoxose acceptor was planned in a different manner. We would instead use known alkyne alcohol **147**,[62] which could be cycloisomerized to digitoxose glycal after glycosylation to the disaccharide unit.

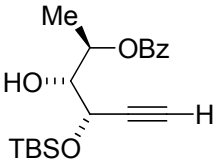
Figure 2.3: Brønsted Acid-Promoted Glycosylation Partners



209

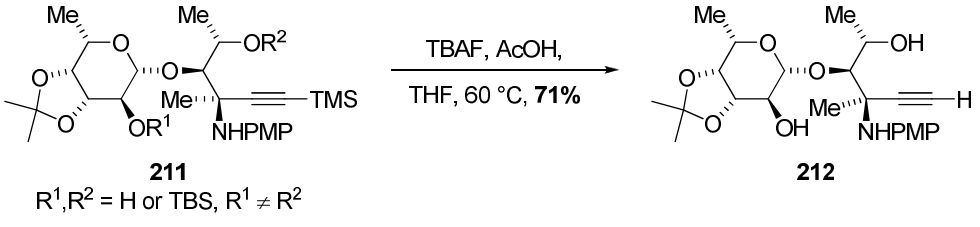


210



147

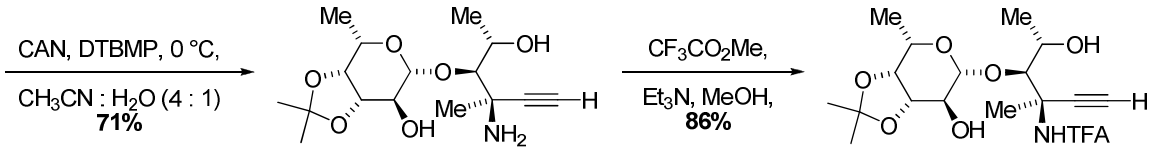
Scheme 2.22: Synthesis of Trifluoroacetamide Analogue **86**



211

R^1,R^2 = H or TBS, $R^1 \neq R^2$

212



213

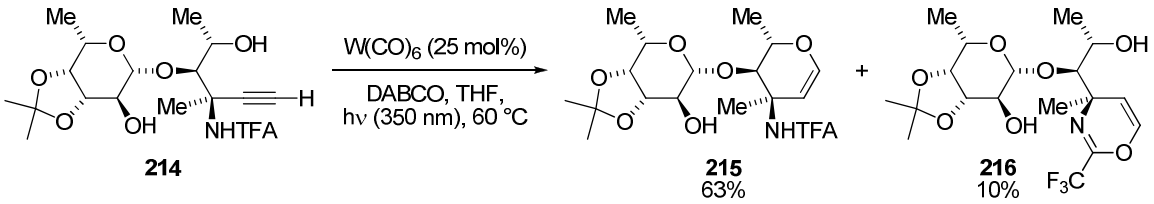
214

The modified disaccharide **209** was synthesized first (scheme 2.22). In order to install the amide, the synthesis had to be taken back to the secondary alcohol **174**. However, it was discovered that the silyl ether migrated while the compound was stored, such that a mixture of silyl ethers was obtained (**211**). This problem was easily solved by removing the silyl groups before exchanging the amine substituent. Re-ordering these steps proved to be advantageous as TBAF could now be used for desilylation without hydration of the alkyne. This decreased the reaction time to 28 hours, compared to 7 days using TBAT. Presumably the electron rich *p*-methoxyphenyl group inductively increased the electron density in the alkyne sufficiently to avoid hydration under the basic

conditions. Oxidative cleavage of the aryl group followed by amide formation using methyl trifluoroacetate provided alkyne alcohol **214**.

The tungsten-catalyzed cycloisomerization of trifluoroacetamide analogue **214** was met with an unexpected outcome (scheme 2.23). When exposed to the same isomerization conditions as the acetamide analogue **178**, some glycal **215** was produced, but in low yield. Surprisingly the trifluoroacetamide now competed as nucleophile for the tungsten vinylidene intermediate, generating the unanticipated 4H-1,3-oxazine **216**. Despite our group's extensive work with tungsten-catalyzed cycloisomerizations, this was the first time we had ever identified an oxazine product.

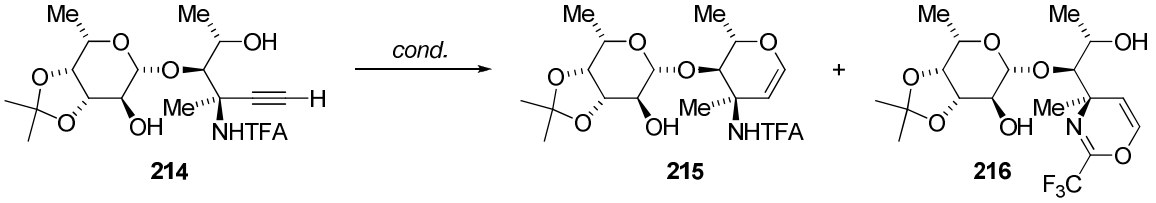
Scheme 2.23: Formation of Glycal and Unexpected 4-H-1,3-Oxazine **216**



In trying to optimize the cycloisomerization, tetrahydrofuran was replaced by toluene in order to avoid degradation that was observed when THF was used (table 2.6). In doing so the reaction was indeed cleaner and higher yielding, though the ratio of glycal to oxazine was nearly 1:1 (entry 2). Reducing the temperature to 45 °C actually favored oxazine formation (entry 3), and so increasing the temperature might favor glycal **215**. Because the light-promoted procedure was limited to a maximum temperature of 65 °C, pentacarbonyl (methoxymethylcarbene) tungsten was instead used in refluxing toluene. The crude ^{1}H NMR did indeed show a 2:1 ratio favoring glycal formation over oxazine,

but a great deal of degradation occurred and a complex mixture was formed. The results indicated that oxazine **216** was the kinetic product, an observation which could be rationalized if one considers intermediates **218** and **219**, stemming from nucleophilic attack of alcohol or acetamide onto vinylidene **217** (scheme 2.24). The half-chair conformation of **218** suffered from several gauche interactions that **219** did not, which might account for the thermal selectivity observed in the transformation.

Table 2.6. Cycloisomerization of Alkyne Alcohol **214**



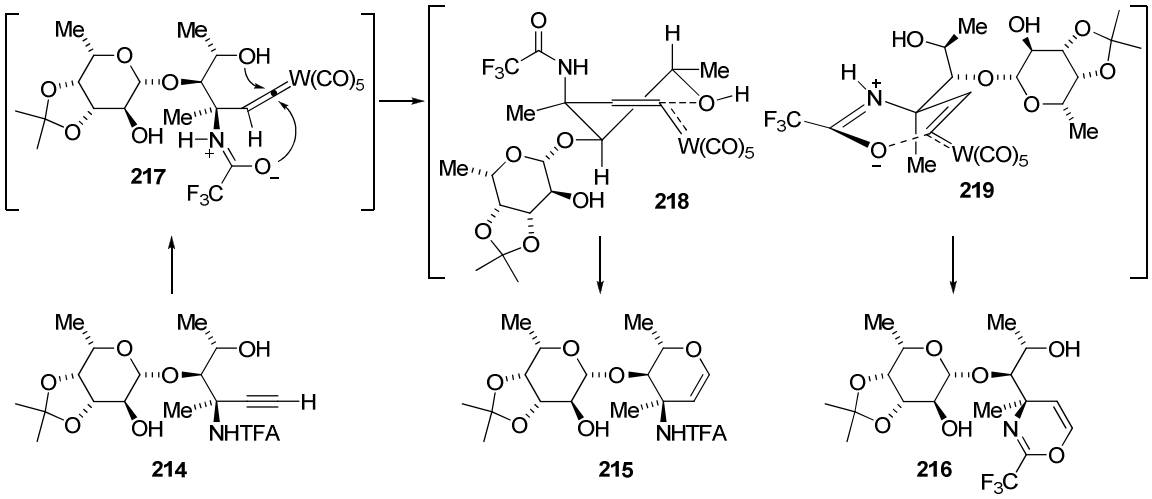
entry	Conditions	% **215**	% **216**
1	$W(CO)_6$ (25 mol%), DABCO, THF, hν (350 nm) 60 - 65 °C	63%	10%
2	$W(CO)_6$ (25 mol%), DABCO, toluene, hν (350 nm) 60 - 65 °C	46%	40%
3	$W(CO)_6$ (25 mol%), DABCO, toluene, hν (350 nm) 45 °C	33%	56%
4	$(OC)_5W{=}C(OCH_3)CH_3$ (25 mol%), DABCO, toluene, reflux	degradation[a]	

[a] The glycal : oxazine ratio was observed to be 2 : 1 in the crude ^{1}H NMR

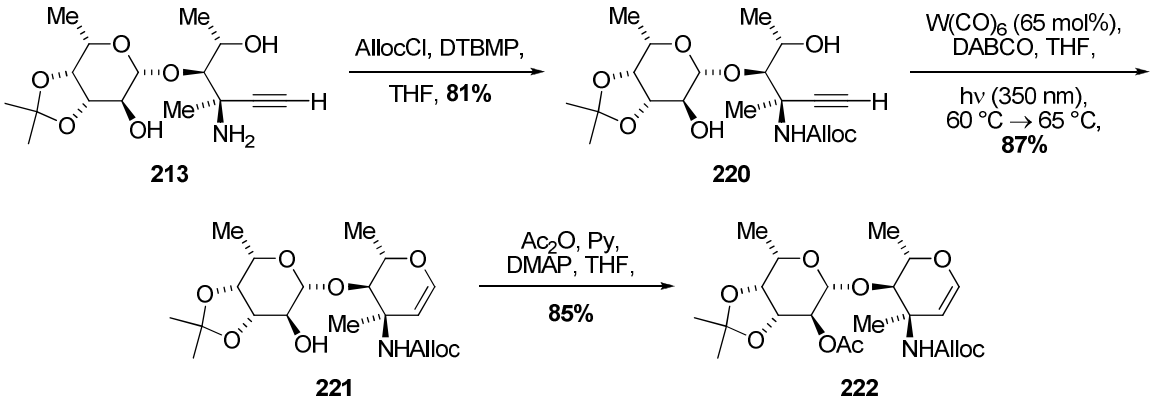
Unfortunately, glycal **215** could not be produced in satisfactory yields, so an alternative amine protecting group was again required. With amine diol **213** previously prepared, it was easy to install new protecting groups immediately before cycloisomerization. An Alloc group was chosen to be tried next. Alloc

groups have been utilized and deprotected on a number of complex oligosaccharides,[101,102] as well as the related vancosamine pyranoside in the course of synthetic work on vancomycin.[103] We reasoned that the pendant nature of the allyloxycarbonyl would allow it to be removed from the congested amine late into the synthesis. Thus an Alloc group was incorporated using allyloxycarbonyl chloride to provide alkyne alcohol **220** (scheme 2.25).

Scheme 2.24: Oxazine Versus Glycal Formation



Scheme 2.25: Preparation of Final Glycosyl Donor



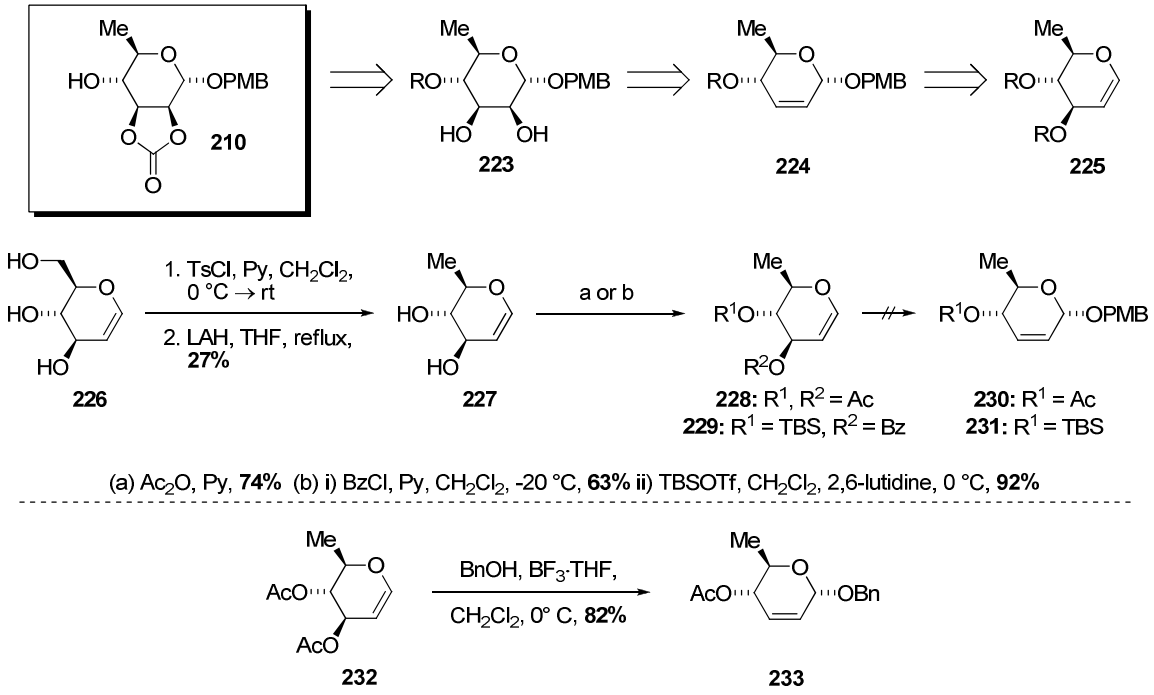
However, the cycloisomerization of **220** did not occur as easily as previous examples. The transformation was much slower than it was for acetamide **178**, and would appear to stall over time. Ultimately, the catalytic loading had to be increased to 65 mol % in order to achieve complete conversion. Neither competing cycloisomerization of the carbamate, nor exo-product was observed. No deleterious side reaction from the Alloc olefin was seen, though several reactions with olefins are known.[71,104,105] It might then be that the Alloc olefin competed with alkyne for tungsten, slowing the rate of reaction. The delay in vinylidene formation would have allowed more opportunities and more time for the tungsten catalyst to degrade. Increasing the catalytic loading was sufficient to overcome this problem. Final acetylation of the fucosyl-C2-hydroxyl provided glycal **222** as the fully prepared glycosyl donor.

Synthesis of both the rhamnose and digitoxose monomers was next required, starting with rhamnose. The desire for the alternately functionalized analogue **210** opened the opportunity for a different and perhaps more efficient synthesis. Thus it was conceived that **210** would be prepared from diol **223** (scheme 2.26). Dihydroxylation to form **223** from preceding olefin **224** might be carried out, as there is excellent precedence for the transformation.[106-108] The olefin could be synthesized by a Ferrier rearrangement[109] of an appropriate rhamnal analogue **225**.

As D-rhamnal is not commercially available, it was quickly synthesized from D-glucal by a known two-step tosylation, reduction process.[110] Rhamnal was then protected either as the diacetate **228** or the C3-benzoate, C4-silyl ether

229.[111] Despite ample precedence for Ferrier rearrangements with rhamnal,[109,112-115] coupling with *p*-methoxybenzyl alcohol did not proceed well. Use of a variety of Lewis acids including BF_3·THF, $InCl_3$, $SnCl_4$, and silica all failed to provide the desired rearrangement in a reproducible way. The problem resided in the incompatibility of PMBOH under the Lewis acidic reaction conditions, which typically failed to react or otherwise seemed to polymerize by crude ^{1}H NMR analysis. When benzyl alcohol was used instead, the Ferrier product **233** was produced smoothly, though this functionality was not of interest.

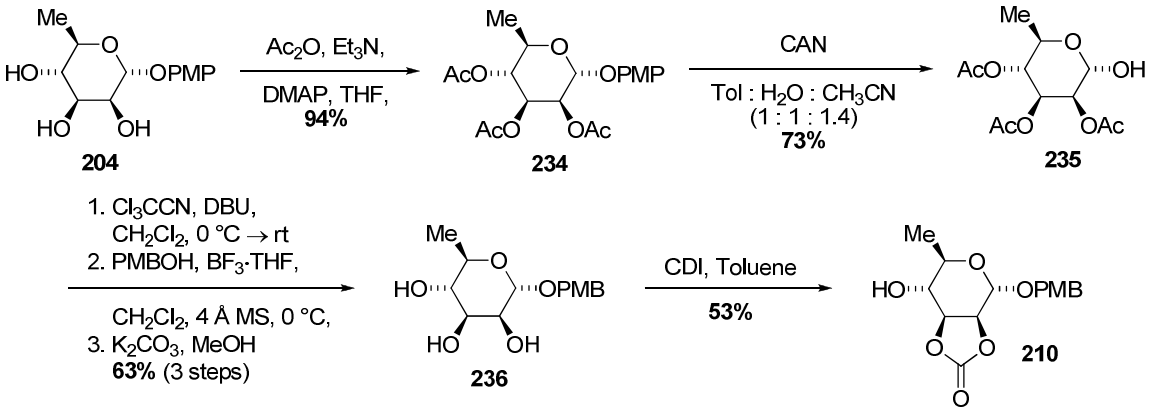
Scheme 2.26: Attempted Rhamnal Based Synthesis of **210**



As the Ferrier rearrangement route had failed to afford C1-*p*-methoxybenzyl analogue **224**, we decided instead to modify our existing D-rhamnose synthesis (scheme 2.27). Triol **204** was first acetylated using acetic anhydride and the *p*-methoxyphenyl group cleaved oxidatively. The solubility of **234** greatly impacted the PMP removal, and a mixture of acetonitrile, water, and

toluene produced the best results. The *p*-methoxybenzyl substituent was then installed by a Schmidt glycosylation protocol, first forming a trichloroacetimidate, then glycosylation promoted by boron trifluoride. Excess *p*-methoxybenzyl alcohol used in the glycosylation could not be separated from product until after deacetylation, providing rhamnoside **236** in 63% over three steps. Condensation of the C2- and C3-hydroxyls with 1,1´-carbonyldiimidazole provided desired glycosyl acceptor **210**. With the rhamnoside prepared, the digitoxose analogue was next synthesized.

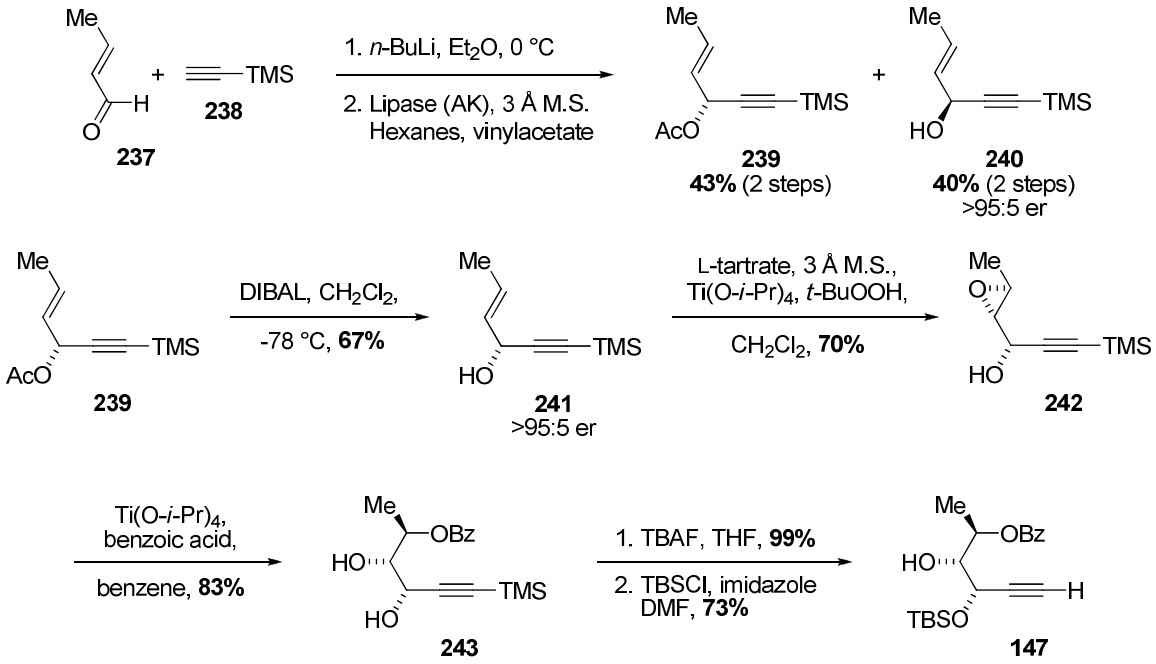
Scheme 2.27: Synthesis of D-Rhamnoside Glycosyl Acceptor



The digitoxose portion was to be glycosylated not as a pyranoside, but as the alkyne alcohol precursor **147** (scheme 2.28). Crotonaldehyde was reacted with lithium acetylide to form a racemic propargylic alcohol which was then resolved using lipase AK. Alcohol **241** was formed after deacetylation of **239** with DIBAL, and the enantiopurity of both **240** and **241** were confirmed by Mosher ester analysis. Sharpless epoxidation next provided epoxide **242** which was then opened using titanium isopropoxide in the presence of benzoic acid.

Removal of TMS using TBAF, and regioselective protection of the propargylic alcohol as a TBS silyl ether provided glycosyl acceptor **147**.

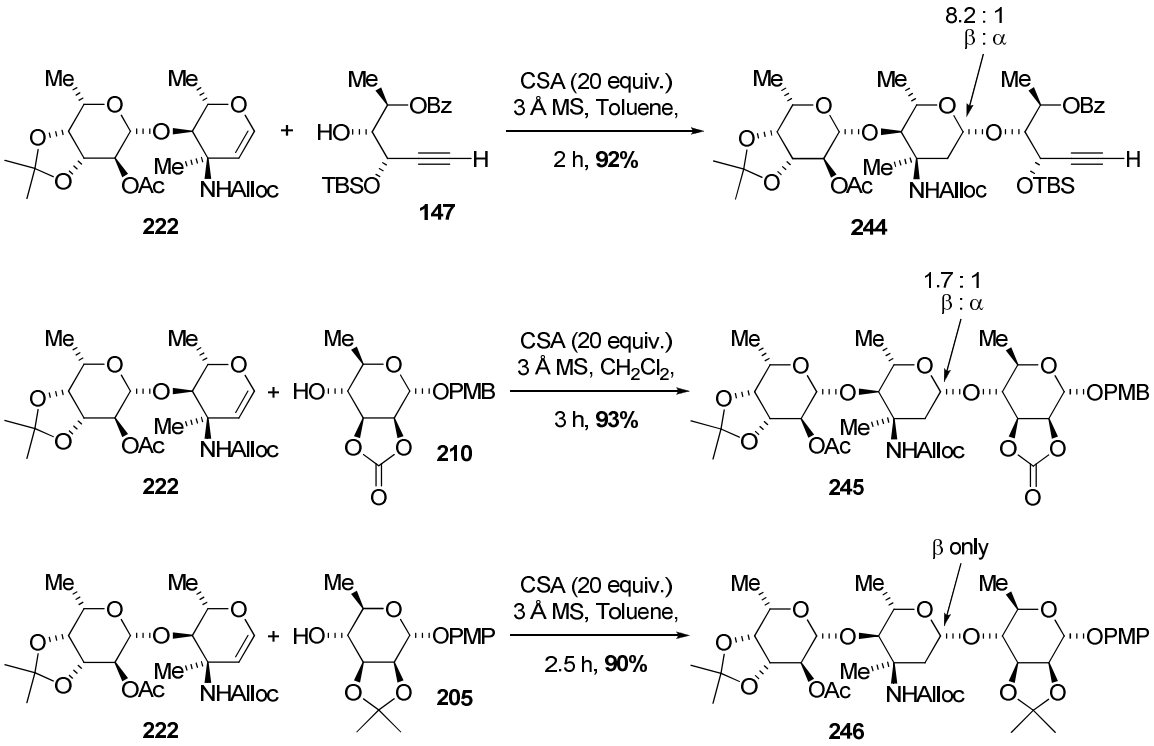
Scheme 2.28: Synthesis of Alkyne Alcohol Glycosyl Acceptor **147**



With all of the glycosylation coupling partners in hand, the Brønsted acid-promoted glycosylations of glycal **222** could be explored (scheme 2.29). Initial attempts to couple alcohol **147** with the saccharosaminyl glycal using substoichiometric amounts of (+)-camphor-10-sulfonic acid indeed provided the desired glycoside, favoring the β-anomer. Unfortunately, the glycosylation conditions also tended to result in hydration across the glycal double bond, which may have been exacerbated by the small reaction scale used during optimization. Addition of 3 Å molecular sieves avoided problems with hydration, though the basicity of the sieves made it necessary to use several equivalents of CSA. The yield of the glycosylation was greatly improved under these conditions providing glycoside **244** in 92% overall, 82% as the desired β-anomer. It is also

worth noting that of three equivalents of **147** used in the glycosylation, the excess was recovered during purification, accounting for 98% of the material. Trisaccharide **244** relates to fucose-12, saccharosamine-11, and digitoxose-10 in saccharomicin B.

Scheme 2.29: Brønsted Acid Glycosylations of Saccharosaminyl Glycal **222**



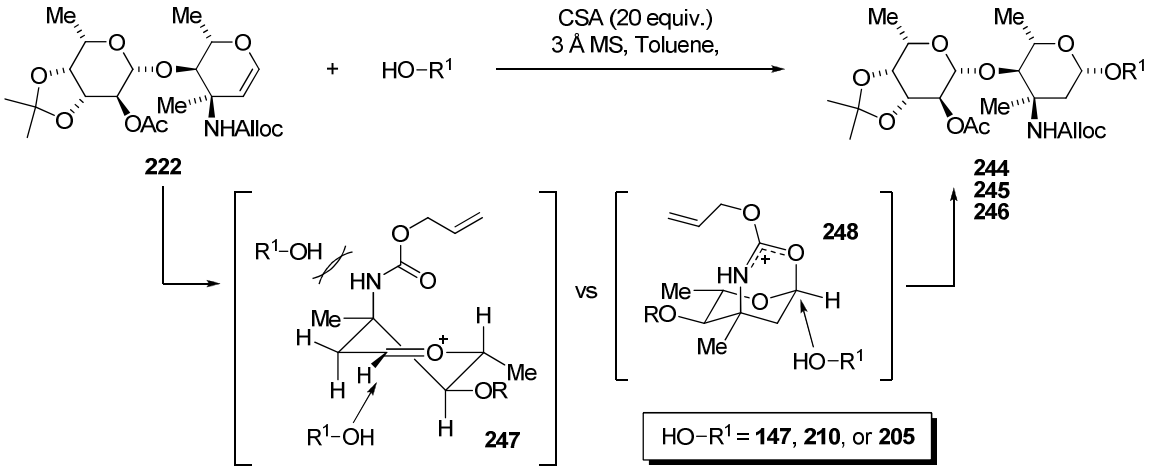
Coupling with a D-rhamnoside acceptor was also pursued, which would provide a trisaccharide motif relating to fucose-8, saccharosamine-7, and rhamnose-6 in saccharomicins A and B, and fucose-12, saccharosamine-11, and rhamnose-10 in saccharomicin A. Rhamnoside **210**, orthogonally protected as a C2-C3 carbonate, was glycosylated using similar conditions to those used for **147**, though this time using dichloromethane, as rhamnoside **210** was insoluble in toluene. The overall yield was again excellent though with diminished

selectivity, providing the β-glycoside **245** in a 1:1.7, α : β ratio. The difference in selectivity could be due simply to the difference in steric and stereospecific interactions of acceptors **147** and **210** with the oxonium intermediate derived from glycal **222**. The selectivity difference could also be the result of solvent effects, with perhaps toluene coordinating to the oxonium intermediate more closely than dichloromethane, and thus influencing the stereochemical outcome. To this end, rhamnoside **205** was instead glycosylated, again in toluene. As with the previous examples the yield of trisaccharide **246** was also excellent, and this time formed exclusively the desired β-anomer.

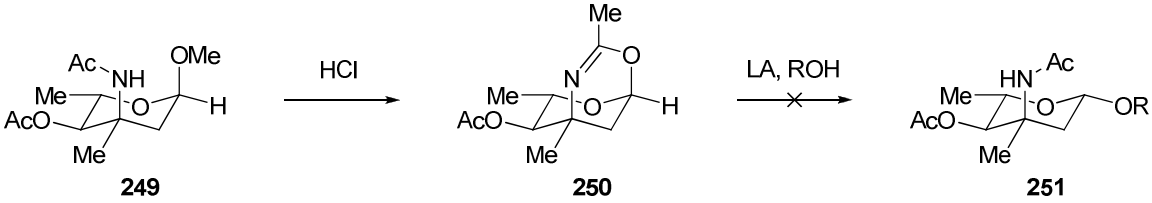
The overall β-stereoselectivity observed in the Brønsted acid-promoted glycosylations could be explained by either asymmetric induction (**247**) or neighboring group participation (**248**) (scheme 2.30). Selectivity induced by participation of the carbamate presented a rational and attractive mechanism, as the carbonyl is six atoms away from the C1-position of saccharosamine, and could form a stable bicyclic intermediate. Nucleophilic attack of the glycosyl acceptor would then open intermediate **248** to provide the β-glycoside. While examples of C3-assisted glycosylations are known,[116-118] studies carried out on the synthesis of cororubicin place this pathway somewhat in doubt (scheme 2.31).[56] During the synthesis of an L-decilonitrose β-glycoside, pyranoside **249** was converted into bicyclic **250** under strongly acidic conditions. The acetal was found to be remarkably robust and failed to behave as a glycosyl donor under a wide array of Lewis acid-promoted conditions. A similar result was also observed

on a related vancosamine analogue, where the acetal intermediate again did not serve as a competent glycosyl donor.[119]

Scheme 2.30: Stereocontrol of the Brønsted Acid-Promoted Glycosylation



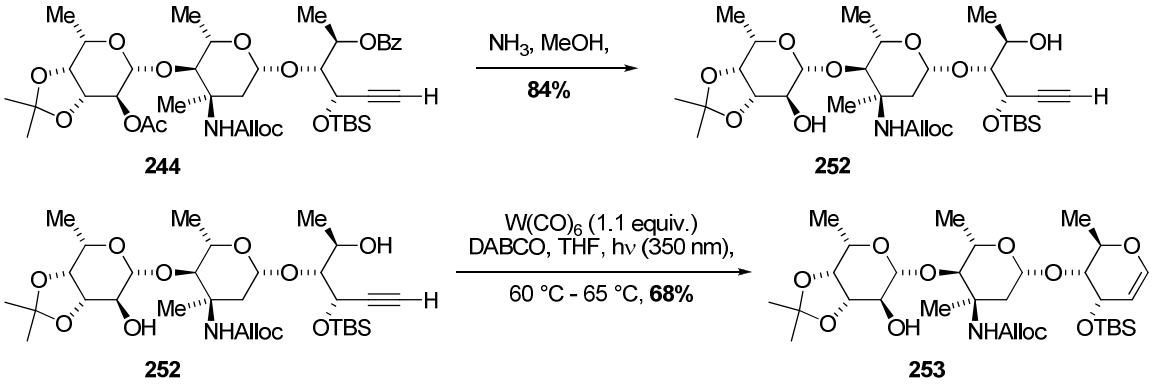
Scheme 2.31: Incompatibility of Neighboring Group Participation



Though neighboring group participation of the carbamate (**248**) cannot be entirely ruled out, it might be that stereoelectronic interactions were responsible for the selectivity of the glycosylations. Consideration of the half-chair asymmetric induction model **247**,[120] which lacked C2-substitution and possessed a C3-quaternary center, made selectivity based primarily on steric interactions appear unlikely. Selectivity was better rationalized by a stereoelectronic interaction, in which Coulombic repulsion between the C3-carbamate and the

hydroxyl of incoming nucleophile directed attack to the pyranoside face opposite the nitrogen. The stereochemical outcome of the glycosylations were probably further impacted by the asymmetric glycosyl acceptors.

Scheme 2.32: Synthesis of Digitoxose Glycal **253**

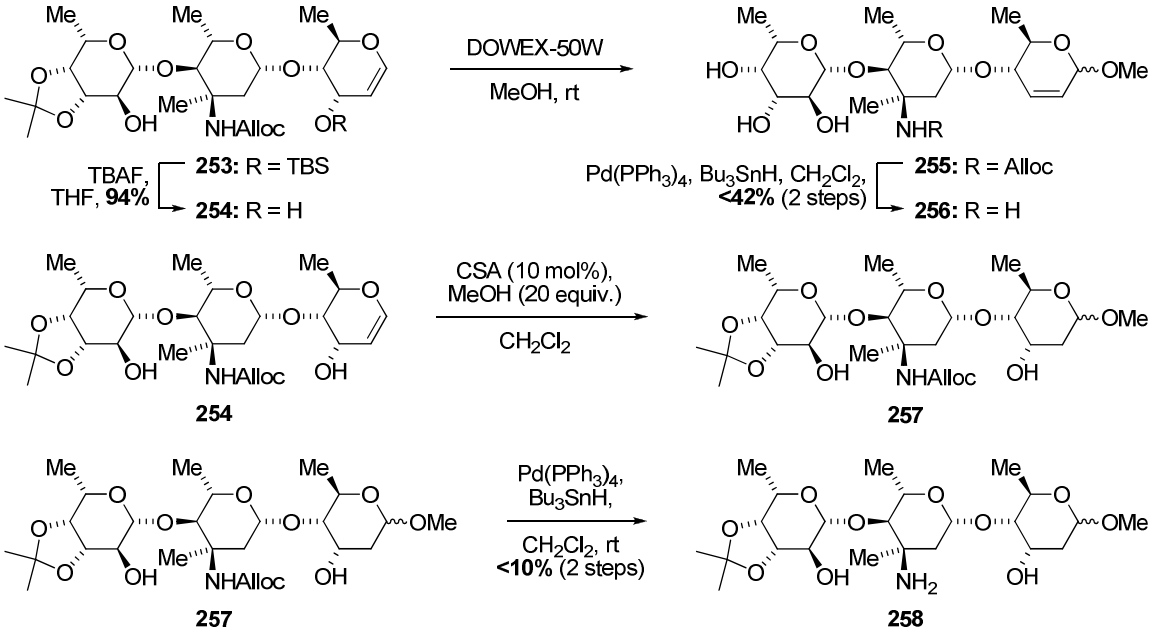


The L-fucose-L-saccharosamine-D-rhamnose trisaccharide has at this point been assembled. The digitoxose analogue however, still required cycloisomerization to access the digitoxose glycal (scheme 2.32). The ester groups of glycoside **244** were deprotected using ammonia in methanol, which provided alkyne alcohol **252**. The cycloisomerization was carried out, and as with glycal **221** additional tungsten hexacarbonyl was required to drive the isomerization to completion. The desired digitoxose glycal **253** was produced in 68% yield, with only a small amount of starting material remaining (6%). The exo-product was observed in the crude reaction mixture (~11% by ^{1}H NMR), but could not be isolated due to its instability.

Trisaccharides **245** and **253** both represented potential building blocks for the assembly of larger segments of the saccharomicins. As planned, each trisaccharide was incorporated with an orthogonal functionality on both the reducing end, and the terminal fucosyl C3,C4-hydroxyls. While these glycosides

were themselves important targets, it was also of interest to fully deprotect **253** and converted the glycal to a methyl glycoside in order to compare the synthetic structure to degradation product **136**. This process proved to be more difficult than expected.

Scheme 2.33: Attempts to Deprotect **253**



From our previous experience with disaccharides **194** and **184**, it was envisioned that the acetonide of **253** could also be removed with DOWEX acidic resin in methanol, with concomitant installation of the methyl glycoside. The deprotection of TBS silyl ethers is also known to occur under these conditions,[121] and it was hoped that all three transformations could be performed in the same reaction. However, when glycal **253** was exposed to DOWEX-50W in methanol silyl ether elimination product **255** was produced as the major product, along with a complex mixture (scheme 2.33). Identification of the elimination product was aided by removal of the Alloc group, which provided glycoside **256** (containing

some inseparable tributyltin byproduct). In an attempt to avoid the elimination, desilylation was carried out using TBAF to provide glycal **254**. Unfortunately, elimination was again observed when the glycoside was exposed to DOWEX resin.

The methyl glycoside could be established when glycal **254** was exposed to a more mild acid (camphorsulfonic acid) in a non-polar solvent. This time the acetonide remained intact, and both the methyl glycoside **257** and the elimination product were produced in a 2.6 : 1 ratio. It may be that the elimination product could be further reduced by decreasing the equivalents of methanol. The Alloc group was again removed to provide trisaccharide **258**, though in low yield over the two steps (less than 1 mg of **258** was isolated, which also contained some inseparable tributyltin byproduct). Unfortunately, a shortage of material prevented further optimization or investigation. It was worth noting that the Alloc group was able to be removed from both analogues **255** and **257**, though the acetonide appeared to be too robust for the trisaccharide structure.

Despite the late stage difficulties, the synthetic studies performed here had met several important goals. The congested linkage to the C4-saccharosamine hydroxyl was established by an early glycosylation to a β-lactam precursor. The racemic nature of the β-lactam provided access to both the L-fucose-D-saccharosamine and L-fucose-L-saccharosamine disaccharides. Comparison of these diastereomers to a degradation product isolated from saccharomicin B demonstrated the L-fucose-L-saccharosamine motif to be the antipode of the natural product. The saccharosamine pyranosides were

themselves constructed using our tungsten-catalyzed cycloisomerization methodology.

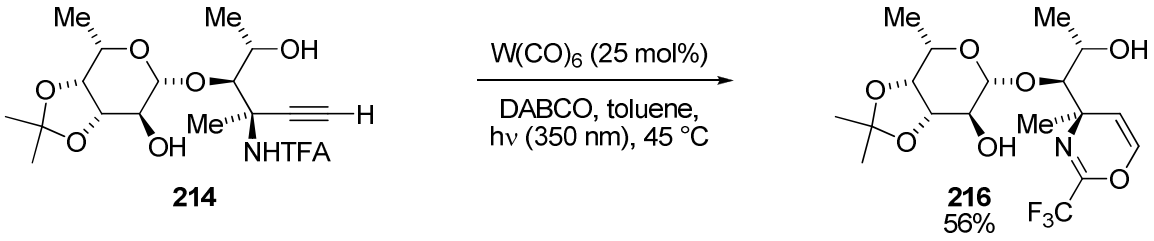
Modification of the L-fucosyl-L-saccharosamine glycal then allowed a Brønsted acid-promoted glycosylation to be explored. Glycosylation to a digitoxose precursor and a rhamnoside analogue both occurred in excellent yield and favored the β-glycosides. The digitoxose-appended trisaccharide was finalized by a late stage cycloisomerization to provide a digitoxose glycal. The final trisaccharides were assembled with orthogonal protecting groups at both their terminal fucosyl units, and the reducing ends. However, the fucosyl acetonide appears to have been too robust to be deprotected from the trisaccharide, and future studies might benefit from an alternate C3,C4-fucosyl protecting group. The synthetic sequence would also benefit from an enantiopure synthesis of the saccharosamine alkyne alcohol.

2.4. Cursory investigation of a tungsten-catalyzed cycloisomerization of propargyl amides, discovered in route to the saccharomicins

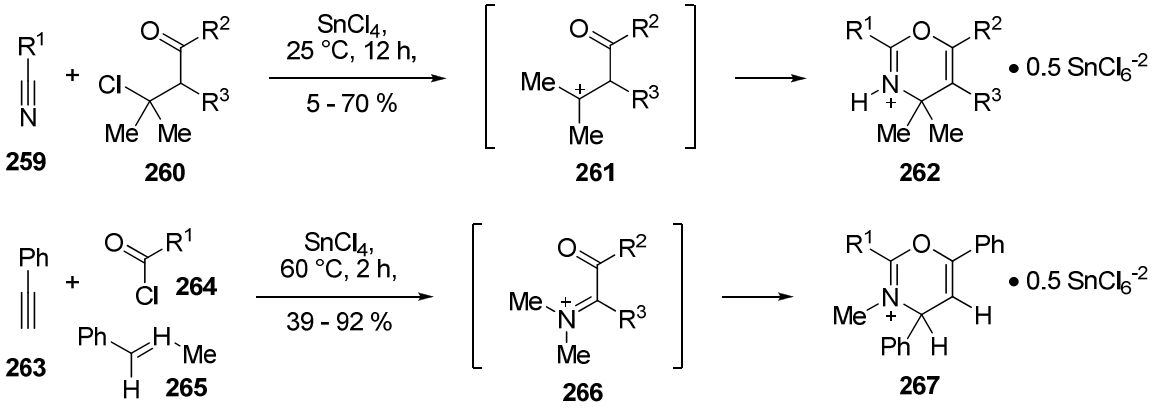
During the course of our work on the saccharomicins, a tungsten-catalyzed cycloisomerization of the alkyne alcohol **214** had surprisingly favored an isomerization to 4-H-1,3-oxazine **216** (scheme 2.34). Despite our considerable work in the cycloisomerization of alkyne alcohols, we had not before observed the formation of an oxazine. Investigation into the literature soon revealed that syntheses of 4-H-1,3-oxazines are quite rare, and their

synthetic utility has not been greatly explored, although these heterocycles have been appeared in two reviews.[122,123]

Scheme 2.34: Discovery of a Tungsten-Catalyzed Cycloisomerization of Propargyl Amides to 4-H-1,3-Oxazines

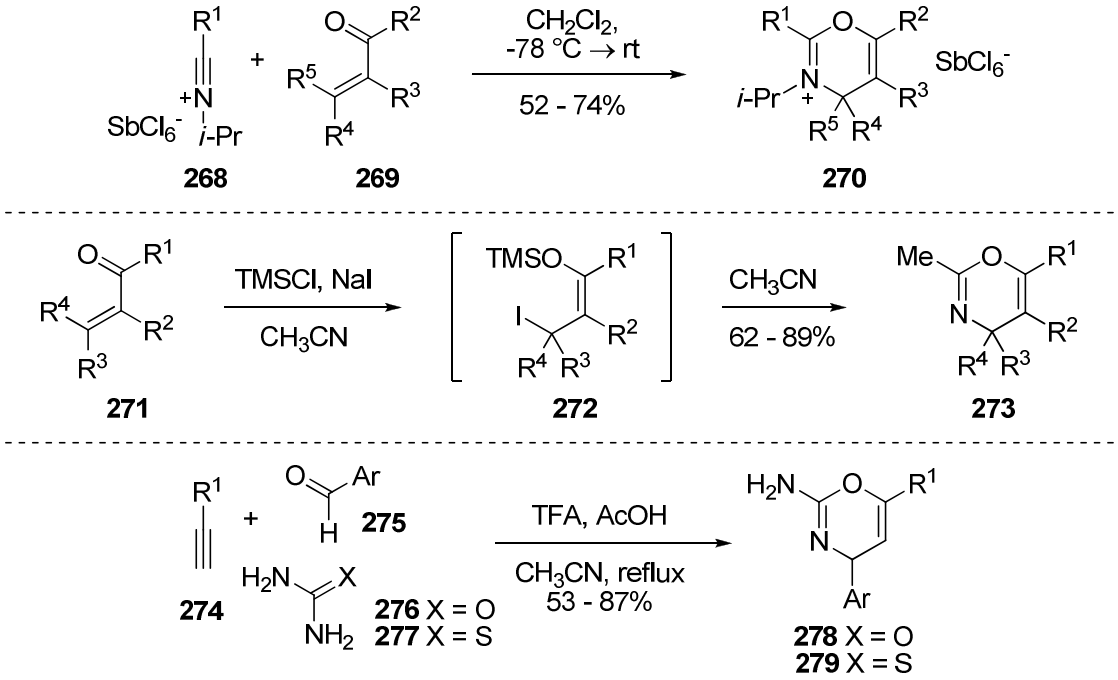


Scheme 2.35: $SnCl_4$ Promoted 4-H-1,3-Oxazine Syntheses



Beyond the reversible dehydration of β-amidoketones under strongly acidic conditions,[124] the first general methods for the preparation of 4-H-1,3-oxazines were developed by Schmidt and Lora-Tamayo (scheme 2.35).[125-127] Tin(IV) chloride promoted cycloaddition of nitrile or alkyne with a β-chloroketone or condensed acid chloride and imine provided the desired oxazines. Oxazines synthesized by these methods were obtained as the tin hexachloride salts.

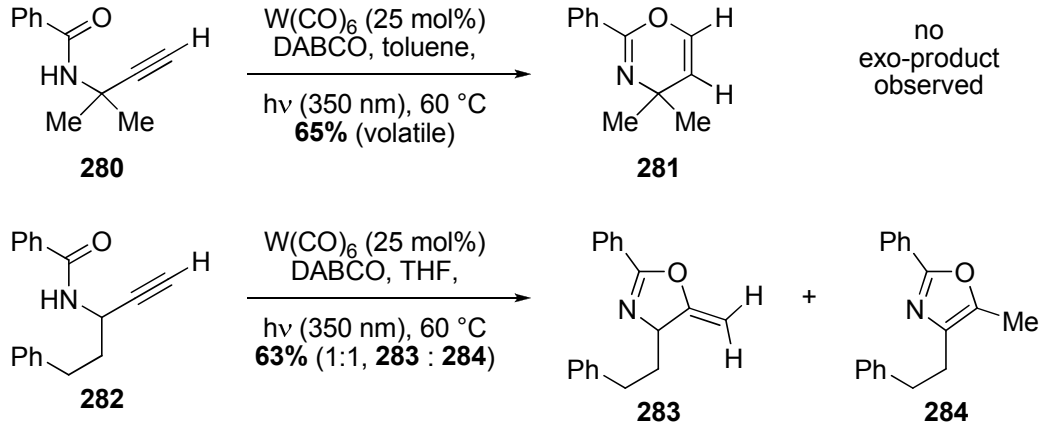
Scheme 2.36: Alternate 4-H-1,3-Oxazine Synthetic Methods



Other methods have since been established, including a related cycloaddition of hexachloroantimonate nitrilium salts (**267**) with α,β-unsaturated ketones (scheme 2.36).[128] The first method that avoided the use of metal salts was developed by Hassner *et al.*, where trimethylsilyl chloride and sodium iodide promoted the cycloaddition between unsaturated ketones and acetonitrile.[129] With the exception of mesityl oxide, this method appeared to be limited to tetrasubstituted olefins. More recently, an acid-promoted, three component cycloaddition was developed for urea and thiourea based analogues.[130] This method also avoided using heavy metal salts, and showed an expanded substrate scope. In addition to the methods listed, a few additional 4-H-1,3-oxazine syntheses have appeared in the literature, though these examples were limited to cases where the oxazine was a byproduct, or formed from one or two very specific substrates.[131-137]

Most of the methods for the construction of 4-H-1,3-oxazines require toxic heavy metal salts, proceed under harsh conditions, and/or suffer from limited substrate scope. If the tungsten-catalyzed cycloisomerization of propargylic amides could be developed into a general method, it would present a mild, catalytic protocol for the syntheses of these oxazines by a novel mechanism.

Scheme 2.37: A Preliminary Test of the Tungsten-Catalyzed Oxazine Reaction

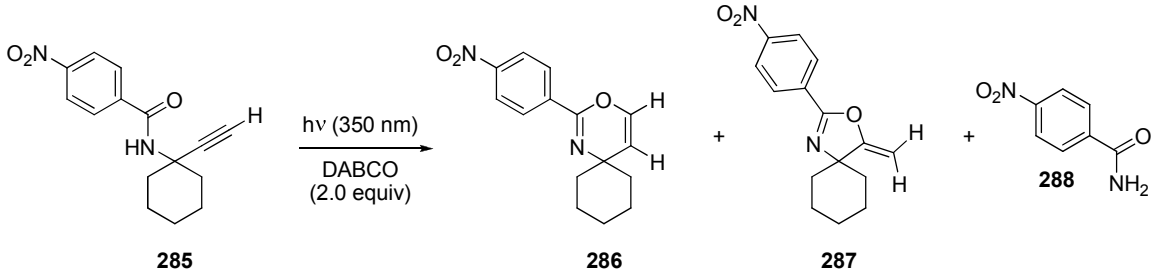


Therefore, test substrates **279** and **281** were prepared from benzoyl chloride and their preceding propargyl amines (scheme 2.37). When exposed to similar reaction conditions as **214**, amide **279** cyclized smoothly to the desired oxazine **280** in 65% yield, with no exocyclic product visible in the crude ^{1}H NMR. The transformation was quite clean and the low yield is suspected to be an artifact of the product's volatility. When amide **281** was tried, the exo-product **282** was the only observed product (**282** readily isomerized to oxazole **283**). The outcome was not entirely surprising, as we have previously noted that ethereal solvents and small substituents at the propargylic position can favor the exocyclic product (see section 1.3.2.) Reaction conditions could be explored which might allow substrates similar to **281** to be isomerized to their corresponding oxazines.

With the encouraging cycloisomerization of **280** in hand, we turned our attentions toward probing the reaction conditions with a more reliable substrate. Propargylic amide **284** was prepared from 4-nitrobenzoyl chloride and the preceding amide for this purpose. The cyclohexane ring provided a fully substituted propargylic center which would favor endo-cyclization as well as provide extra mass to reduce product volatility. The *p*-nitrobenzoyl amide also provided additional mass, and more closely mimicked the trifluoroacetamide of which the reaction was discovered than did phenyl.

The cycloisomerization of **284** was explored by variation of catalytic loading, reaction temperature, and solvent (table 2.7). The same reaction conditions used for the isomerization of **214** were tried first (entry 2) and provided a base line yield for oxazine **286**. When the catalytic loading of tungsten hexacarbonyl was lowered to 10 mol %, the reaction proceeded in lower yield of oxazine **286** and some starting material remained even after 18 hours. A notable amount of amide **287** was also formed and seemed to increase in quantity over time by TLC analysis. Increasing the catalytic loading to 35 mol % (entry 3) and then 45 mol % (entry 4) consistently improved the yield of the oxazine and shortened the reaction time. Reducing the temperature (entry 5) did not affect the reaction outcome other than increasing the necessary reaction time. Finally, switching to THF as solvent (entry 6) greatly reduced the yield of oxazine **286**, and for the first time the exo-product was observed. Likely, ethereal solvent increased the nucleophilicity of the amide allowing exo-cyclization to begin competing with vinylidene formation.

Table 2.7: Exploration of Oxazine Formation Conditions



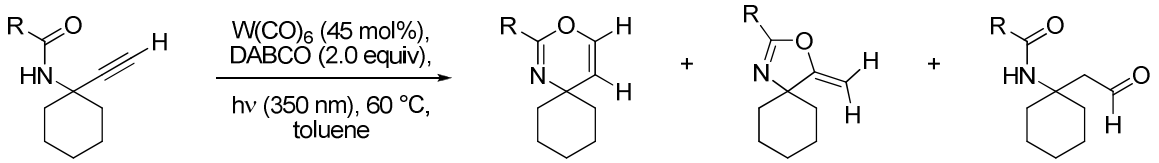
285 **286** **287**

entry	solvent	mol % $W(CO)_6$	temp. (°C)	time	% 285	% 286	% 287	% 288
1	toluene	10%	60 °C	18 h	**19%**	**60%**	**-**	**17%**
2	toluene	25%	60 °C	2.5 h	**29%**	**69%**	**-**	**-**
3	toluene	35%	60 °C	5.0 h	trace	**78%**	**-**	trace
4	toluene	45%	60 °C	3.5 h	trace	**83%**	**-**	trace
5	toluene	45%	30 °C	5.0 h	trace	**84%**	**-**	trace
6	THF	45%	60 °C	3.5 h	trace	**49%**	**17%**	**10%**

With the effect of some of the reaction conditions better understood, the substrate scope was next probed, using the conditions of entry 4 (table 2.7) as an initial standard protocol to compare amide substituent effects (table 2.8). Compared to the *p*-nitrophenyl analogue (entry 1), substitution to phenyl (entry 2) provided a quantitative yield, and now showed a modest amount of exo-cyclization. Increased electron density of the aryl moiety (entry 3) not surprisingly also increased the yield of the exo-cyclic byproduct due to the increased nucleophilicity of the amide. It is worth noting that all of the aryl

amides were stable to column chromatography and could be isolated in good yield.

Table 2.8: Amide Substrate Scope



289 **290** **291** **292**

Entry	R	time	% 290[a]	% 291[a]	% 292[a,b]
1	O_2N—	3.5 h	**83%**	**-**	-
2		4.5 h	**96%**	**4%**	**-**
3	MeO—	1 h	**80%**	**14%**	**-**
4	*t*-Bu—	2 h	**-**	**-**	**77%[c]**
5		1 h	**12%**	**12%**	**56%[d]**
6	F_3C—	2.0 h	**<1% [e]**	**-**	**-**

[a]Isolated yields after column chromatography. [b]The aldehyde product was formed from some analogues by ring opening during purification by column chromatography. [c]Crude ^{1}H NMR showed only cyclization products, 7.1 : 1 endo:exo. [d]Crude ^{1}H NMR showed only cyclization products, 3.4 : 1 endo:exo. [e]Amide was converted cleanly to the endo product by ^{1}H NMR, although the product could not be isolated due to its volatility.

Alkyl amides were also found to be compatible with the transformation (entries 4 and 5). Both of the *tert*-butyl and hydrocinnamoyl analogues

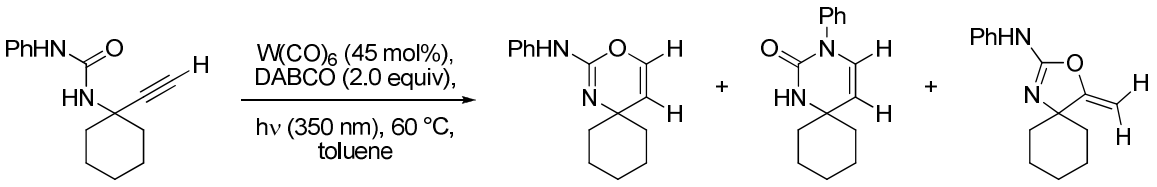
preferentially formed 4-H-1,3-oxazines with 7.1:1 and 3.4:1 endo:exo ratios respectively. When exposed to lewis acidic conditions during column chromatography, both of these alkyl analogues readily underwent ring opening to their related β-amido aldehydes. Chromatography on a basic solid phase might avoid the ring opening. However, the ring opening is a useful transformation, and it is interesting that the oxazine or the aldehyde might be selected for in a single step by choosing the appropriate amide. A trifluoroacetamide (entry 6) also provided oxazine by ^{1}H NMR of the crude reaction mixture. Unfortunately, the product was extremely volatile, such that even dichloromethane could not be removed without substantial loss of material, and purification by chromatography was impossible.

Among these examples, exo-cyclization was sometimes a significantly competing product, especially for the alkyl examples. The reaction might be optimized to avoid these byproducts in a number of ways. Decreasing the reaction temperature, while slowing vinylidene formation, would also presumably slow the nucleophilic attack of the amide on the alkyne. Altering both the identity and loading of the amine base might provide a more pronounced effect. We have previously observed that changing the identity of the amine base can affect the outcome of our alkyne alcohol cycloisomerizations,[62,63] and the same affect might hold true for oxazines. In this case, use of Hunig's base, or lutidine might slow the deprotonation of the amide, thus decreasing its nucleophilicity and favoring oxazine formation. Using only catalytic amounts of amine base has also

been shown to favor 6-endo-cyclization in alkyne alcohol isomerizations, and so might be useful in this transformation as well.[71]

Another interesting isomerization was carried out using urea **293** (scheme 2.38). When exposed to the same reaction conditions as those presented in table 2.8, urea **293** formed a mixture three isolable products including 2-amino-4-H-1,3-oxazine **294**, cyclic-urea **295**, and exo-cyclic byproduct **296**. Formation of the oxazine and the cyclic-urea presents an interesting opportunity, as tuning the electronic character of the substituents on the terminal nitrogen might allow selective formation of products similar to **294** and **295**. The exo-cyclic byproduct might be avoided by altering conditions as discussed above.

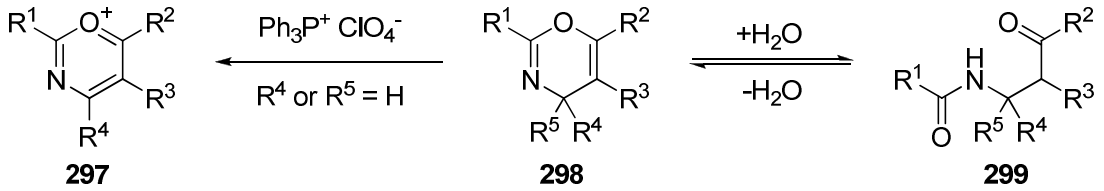
Scheme 2.38: Cycloisomerization of Propargylic Urea **293**



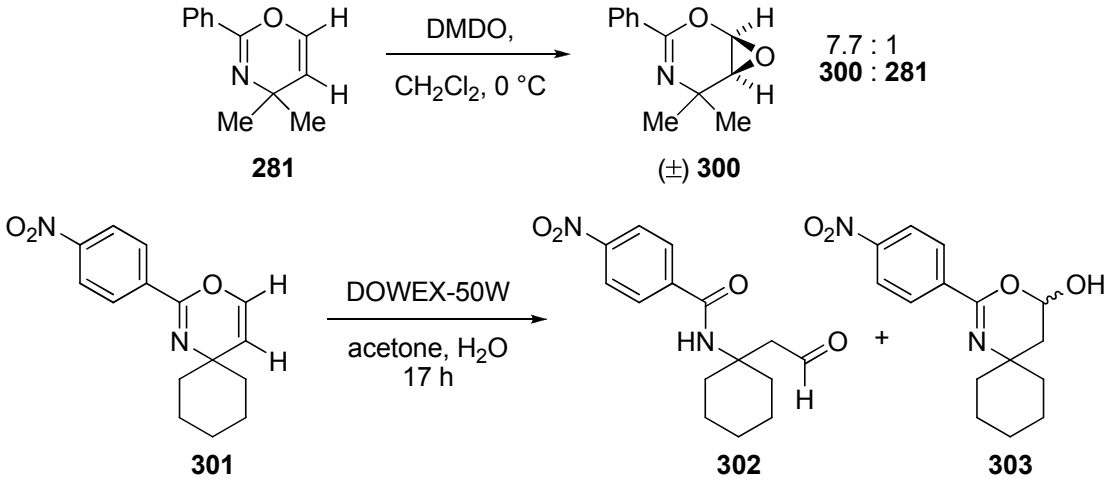
The synthetic utility of 4-H-1,3-oxazines have not been extensively explored, and to date remain limited to ring opening under strongly acidic conditions or conversion to oxazinium salts (scheme 2.39).[123] It was of interest then to explore further reactions that would expand the utility of this class of oxazines. Toward this purpose, two preliminary transformations have been demonstrated, although not yet optimized (scheme 2.40). Reaction with DMDO cleanly provided epoxide **295**, along with some remaining starting material. While ring opening to stable aldehydes was accomplished by chromatographing

alkyl amide derived oxazines over silica gel, analogue **285** was also ring opened by using DOWEX resin. This method is far mormild than hydrochloric acid used in previous studies.

Scheme 2.39: Previously Explored Synthetic Uses of 4-H-1,3-Oxazines



Scheme 2.40: Exploration of 4-H-1,3-Oxazine Synthetic Utility



While the substrate scope explored thus far remains modest, the preliminary results are encouraging. Variation of the propargylic position is of particular interest, which if combined with the enantiopure synthesis of propargyl amines[138,139] could provide enantiopure oxazines. The synthetic potential of these heterocycles warrants further investigation, and the biological activity of 4-H-1,3-oxazines is likely also of interest to explore.

3. Experiments

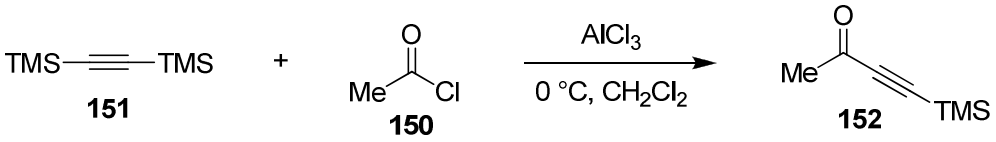
3.1. Experimental procedures

General: ^{1}H and ^{13}C spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C), an Inova-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), a Unity-600 spectrometer (600 MHz for ^{1}H, 150 MHz for ^{13}C), or an Inova-600 spectrometer (600 MHz for ^{1}H, 150 MHz for ^{13}C). NMR spectra were recorded in solutions of deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.27 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR), deuterated methanol (D_3COD) with residual methanol (δ 3.31 ppm for ^{1}H NMR and δ 49.00 ppm for ^{13}C NMR), or deuterated dimethylsulfoxide (δ 2.50 ppm for ^{1}H NMR and δ 39.52 ppm for ^{13}C NMR) taken as the internal standard, and reported in ppm. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; app, apparent. IR spectra were taken on a Mattson Genesis II FT-IR spectrometer as neat films. Mass Spectra (high resolution FAB) were recorded on a VG 70-S Nier Johason Mass Spectrometer. Optical rotations were recorded at 23 ℃ with Perkin-Elmer Model 341 polarimeter. Melting points were recorded on Fischer-Johns melting point apparatus. Analytical Thin Layer Chromatography (TLC) was performed on pre-coated glass backed plates purchased from Whitman (silica gel 60 F_{254}; 0.25 mm thickness). Flash chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from EM Science.

All reactions were carried out with anhydrous solvents in oven-dried and/or flame-dried and argon-charged glassware except in those reactions using

water as reagent or solvent. All anhydrous solvents were dried over activated molecular sieves (beads) and water-content assayed by Karl Fischer titration prior to use. All reagents were purchased from Aldrich Chemical, GFS Chemicals, STREM Chemicals Inc. or prepared as described in the cited literature.

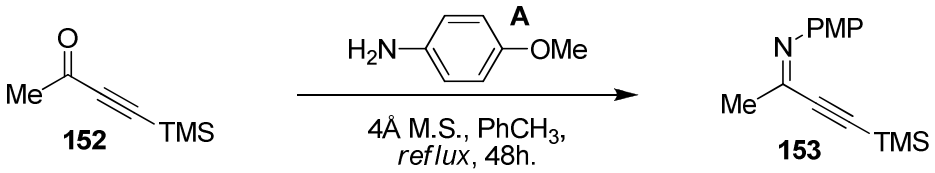
3.1.1. Experimental procedures of section 2.1



4-Trimethylsilyl-3-butyne-2-one 152: A mixture of bis-trimethylsily acetylene (50.0 g, 293 mmol) and acetyl chloride (19.0 mL, 267 mmol) in anhydrous CH_2Cl_2 (534 mL) under argon was cooled to 0 °C and stirred for 5 minutes. Aluminum trichloride (42.7 g, 320 mmol) was added portion wise over 10 minutes. The reaction mixture was stirred at 0 °C under argon for 6 hours. Quenching was carried out with 0.5 M HCl aqueous solution (200 mL) added dropwise at 0 °C over 3 hours (reaction bubbles vigorously), then warmed slowly to room temperature. The resulting biphasic solution was separated and the aqueous layer extracted twice with additional CH_2Cl_2 (2 x 200 mL). The organic fractions were combined and dried over $MgSO_4$ for 15 minutes at room temperature (an unidentified solid percipitate forms with addition of $MgSO_4$, and the solution changes from cloudy gray to dark brown) then filtered. Evaporation followed by distillation under reduced pressure (aspirator, ~40 torr) (b.p. 55 – 70 °C, oil bath temperature 90 – 100 °C) provided 4-trimethylsilyl-3-butyne-2-one **152** (30.3 g,

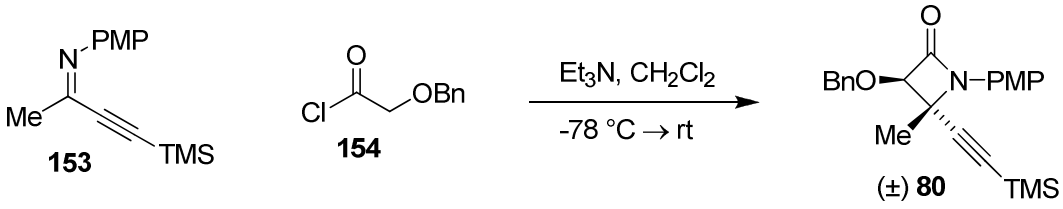
81%) as a clear colorless oil. ^{1}H spectrum of **152** matches that of commercially available material.

IR (neat): 2963, 1678, 1420, 1357, 1253, 1198, 847; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 0.25 (s, 9H).



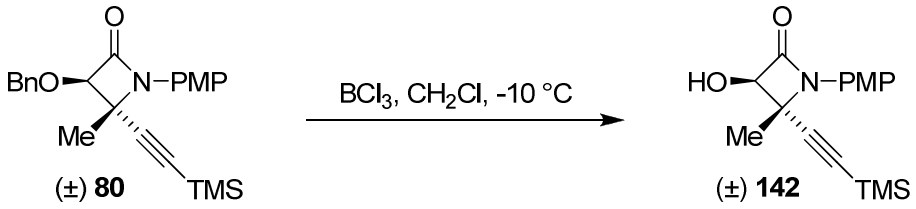
***N-p*-methoxyphenyl-4-trimenthylsilyl-3-butyne-2-imine 153:** 4 Å molecular sieves (440 g) were activated under vacuum in a dry 50 mL round bottom flask, then placed under argon. 4-Trimethylsilyl-3-butyne-2-one **152** (38.3 mL, 273 mmol), *p*-anisidine (40.3 g, 327 mmol), and toluene (560 mL) were added and the reaction heated under argon to reflux. The reaction was refluxed for 24 hours, then cooled to room temperature and more *p*-anisidine (20.4 g, 166 mmol) was added in one portion. The reaction was refluxed for an additional 48 hours. After cooling to room temperature, the reaction mixture was filtered through celite with CH_2Cl_2 (2 × 500 mL). Solvent was removed by vacuo and the resulting crude mixture was purified by column chromatography (9:1, hexanes:ethyl acetate) providing PMP protected imine **153** (37.6 g, 56%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (d, *J* = 9.0 Hz, 2H), 8.86 (d, 9.0 Hz, 2H), 3.82 (s, 3H), 2.34 (s, 3H), 0.12 (s, 9H).



β-lactam 80: To solution of benzyloxy acylchloride (44.86 mL, 276.0 mmol) in CH_2Cl_2 (1.125 L) at –78 °C under argon was added triethyl amine (64.11 mL, 459.9 mmol) dropwise over 20 minutes. (*CAUTION* Reaction will 'smoke' if Et_3N is added too quickly. Perform the addition more slowly if necessary.) *N-p*-methoxyphenyl-4-trimenthylsilyl-3-butyne-2-imine **152** (37.62 g, 153.3 mmol) in CH_2Cl_2 (67 mL) was added slowly to the reaction mixture over 15 minutes at –78 °C. The reaction was allowed to warm slowly to room temperature over 4 h, and stirred an additional 8 h at ambient temperature. The reaction was cooled to 0 °C, quenched with $NaHCO_3$ saturated solution (800 mL), and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL), the organic layers combined, dried over Na_2SO_4 and solvent removed by vacuo. The crude reaction mixture was chromatographed on silica gel using a gradient (98:2 → 95:5 → 9:1 → 85:15 → 8:2, hexanes:ethyl acetate) to provide racemic β-lactam **80** as a clear, viscous oil (37.80 g, 63%).

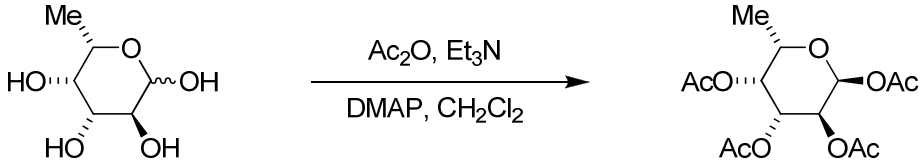
IR (neat) 2958, 2901, 2164, 1758, 1512, 1248, 844 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, J = 9.0 Hz, 2 H), 7.39 (m, 5 H), 6.88 (d, J = 9.0 Hz, 2 H), 4.85 (d, J = 11.4 Hz, 1 H), 4.83 (s, 1H), 4.75 (d, J = 11.4 Hz, 1 H), 3.81 (s, 3 H), 1.64 (s, 3 H), 0.19 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 156.8, 136.8, 129.8, 128.8, 128.5, 128.4, 119.7, 114.5, 104.3, 92.4, 89.3, 74.1, 57.9, 55.7, 20.1, -0.1; HRMS calcd for $C_{23}H_{28}O_3N_1{}^{28}Si$ $[M+H]^+$: 394.1833. Found: 394.1821.



(±) **80** (±) **142**

2-Hydroxy-β-lactam 142: To a dry 1-L flask was added 2-Hydroxy-3-(5-trimethylsilyl) alkynyl-3-methyl-*N*-(*p*-methoxyl phenyl)-β-lactam **80** (37.80 g, 96.06 mmol) in CH_2Cl_2 (480 mL) under argon, and cooled on a ice/brine bath (bath temp -10 ℃) . BCl_3 (1.0 M in Hexanes, 288.2 mL, 288.2 mmol) was added slowly over 30 minutes. The reaction mixture was stirred for 1.5 h then quenched very slowly with H_2O (150 mL, H_2O was cooled on ice-bath prior to use). The organic fraction was separated, washed with 0.5 M HCl solution (250 mL), dried over Na_2SO_4, and solvent removed by vacuo. The crude product was chromatographed (2:1, hexanes : ethyl acetate) to provide α-hydroxy-β-lactam **142** as a fine white powder (25.61 g, 88%).

IR (neat) 3369, 2958, 2901, 2167, 1728, 1513, 1250, 1123, 842 cm^{-1}; ^1H (600 MHz, $CDCl_3$) δ 7.57 (d, J = 9.0 Hz, 2 H), 6.87 (d, J = 9.0 Hz, 2 H), 5.06 (s, 1 H), 3.80 (s, 1 H), 1.73 (s, 3 H), 0.18 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 156.9, 129.6, 119.9, 114.5, 104.0, 92.6, 83.3, 58.7, 55.7, 20.1, -0.1; HRMS calcd for $C_{16}H_{22}NO_3{}^{28}Si$ $[M+H]^+$: 304.1364. Found: 304.1360; Anal. calcd for $C_{15}H_{21}NO_3{}^{28}Si$: C, 63.33; H, 63.15. Found: C, 63.15; H, 7.01.

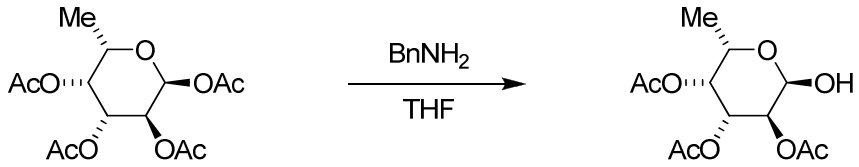


157 **B**

1,2,3,4-peracetoxy-L-fucose B: Commercially available L-fucose (25.0 g, 152 mmol) was dissolved in CH_2Cl_2 (508 mL) with triethyl amine (91.3 mL, 655 mmol) and acetic anhydride (60.5 mL, 640 mmol) at room temperature under argon. The reaction mixture was cooled on an ice bath, and 4-*N,N*-

Dimethylaminopyridine (930 mg, 7.62 mmol) was added in one portion (the reaction mixture warms considerably upon addition of DMAP). After 10 min, the ice bath was removed and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was washed with a saturated solution of $NaHCO_3$ (500 mL) and the aqueous phase was then extracted with CH_2Cl_2 (2 × 300 mL). The organic fractions were combined, dried over Na_2SO_4, and solvent removed by *vacuo*. Crude product could be chromatographed using a 7:3, hexanes : ethyl acetate to provide peracetoxy-L-fucose **B** as a clear, transparent sticky residue in quantitative yield, the α-anomer is strongly favored. Material was typically carried on without further purification. Spectral data of major (α) anomer only:

^1H (600 MHz, $CDCl_3$) δ 6.35 (d, J = 3.0, 1 H), 5.34 (m, 3 H), 4.28 (q, J = 6.0, 1 H), 2.19 (s, 3 H), 2.16 (s, 3 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.17 (d, J = 6.6, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 170.4, 170.2, 169.4, 90.2, 70.8, 68.0, 67.5, 66.7, 21.2, 20.9, 20.8, 16.6, 14.4.

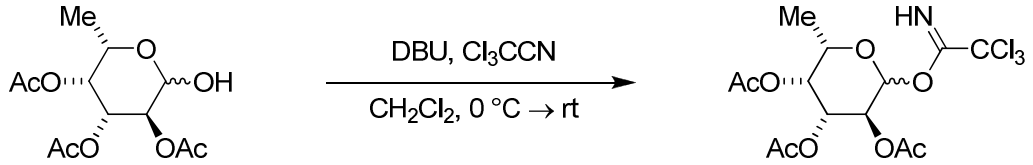


B **158**

1-hydroxyl-2,3,4-triacetoxy-L-fucose 158: 1,2,3,4-peracetyl-L-fucose **B** (50.0 g crude, 152 mmol) was dissolved in THF (380 mL) at ambient temperature in a dry round bottom flask under argon and benzyl amine (18.2 mL, 167 mmol) was added in one portion. The reaction mixture was 19 h, and then quenched with 0.5 M HCl solution (400 mL). The aqueous phase was extracted with ethyl

acetate (3 × 200 mL), the organic fractions were combined, dried over Na_2SO_4, and solvent removed by *vacuo*. Chromatography with 7:3, hexanes : ethyl acetate, provided 1-hydroxy-2,3,4-triacetoxy-L-fucose **158**, favoring the α-anomer, as a sticky white solid (13.70 g, 87% over 2 steps).

IR (neat) 3452, 2986, 2941, 1745, 1228, 1058; ^{1}H (400 MHz, $CDCl_3$) δ 5.48 (d, J = 3.6 Hz, 1 H), 5.41 (dd, J = 3.6, 10.8 Hz, 1 H), 5.32 (dd, J = 1.2, 3.6 Hz, 1 H), 5.16 (dd, J = 3.6, 10.8 Hz, 1 H), 4.42 (dq, J = 0.8, 6.8 Hz, 1 H), 2.98 (bs, 1 H), 2.18 (s, 3 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.15 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 170.6, 170.3, 90.9, 71.4, 68.6, 67.9, 64.7, 21.1, 21.0, 20.9, 16.2; HRMS calcd for $C_{12}H_{18}{}^{23}NaO_8$ $[M+Na]^+$: 313.0894, found: 313.0891.

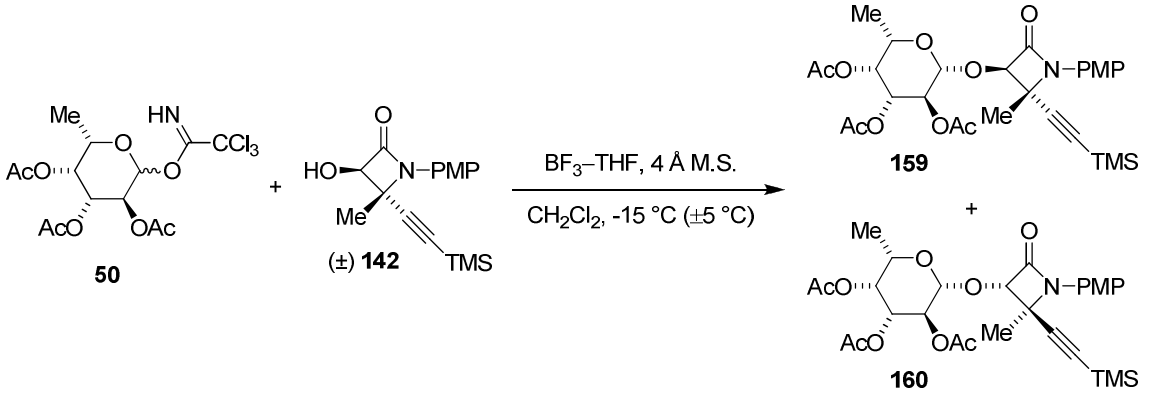


158 **50**

2,3,4-triacetoxy-L-fucosylpyranosyltrichloroacetimidate 50: 1-hydroxyl-2,3,4-triacetoxy-L-fucose **158** (3.00 g, 1.03 mmol) was dissolved in CH_2Cl_2 (35 mL) in a dry 100 mL round bottomed flask at 0 °C (ice bath) under argon. To the solution 1,5-diazabicyclo[5.4.0]undec-7-ene (0.5 mL, 0.31 mmol) was added in one portion and the mixture stirred for 5 min. Trichloroacetonitrile (3.10 mL, 3.10 mmol) was then added dropwise. The reaction mixture was allowed to warm slowly to room temperature over 2-3 h, and stirred overnight (8 – 12 h). The reaction mixture turned a dark brown as the reaction proceeded. The crude solution was then filtered through a short pad of silica gel using ethyl acetate. Solvent was removed and dried under high vacuum (>3 h). Trichloroacetimidate

158 was always checked by ^{1}H NMR, $CDCl_3$ and carried on without further purification.

^{1}H (400 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 6.55 (d, J = 3.2 Hz, 1 H), 5.41 (m, 2 H), 5.35 (dd, J = 3.6, 10.4 Hz, 1 H), 4.37 (q, J = 6.8 Hz, 1 H), 2.19 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 1.18 (d, J = 6.8 Hz, 3 H).

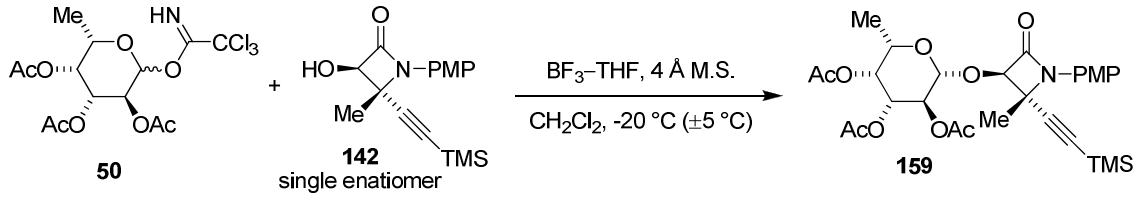


β-lactam glycosides 159 + 160: (As an inseparable mixture of both β diastereomers.)

(Reaction was typically run on the following scale in parallel then combined for purification.) In a dry 25 mL round bottomed flask, under argon, was added activated 4 Å molecular sieves (1.5 g) and racemic β-lactam **142** (285.2 mg, 0.940 mmol) with CH_2Cl_2 (3.4 mL) The reaction mixture of each flask was cooled to -15 °C (maintained at -15 °C (±5 °C) in a dry-ice, acetone bath). Trichloroimidate **50** solution (6 mL, prepared as a 0.172 M solution in CH_2Cl_2) was added and the reaction mixture stirred and additional 10 min to allow for temperature equilibration. Next, 2-3 drops of BF_3-THF were added and the reaction was stirred on acetone bath (-15 °C) for an additional 4 h, then warmed to 0 °C and quenched with $NaHCO_3$ saturated solution (2 mL) under strong stirring. After 10 minutes, the contents of the reaction vessel were filtration

through a pad of celite with ethyl acetate, and solvent was removed by *vacuo*. The crude reaction mixture was chromatographed (9:1 → 85:15 → 8:2 → 7:3, hexanes : ethyl acetate) to provide an inseparable mixture of both β-glycosides **159** and **160** (326.7 mg – 364.4 mg, 60 – 67%) as a sticky, waxy residue. The reaction procedure was performed in parallel and combined for purification to provide 25.31 g (61%) of material.

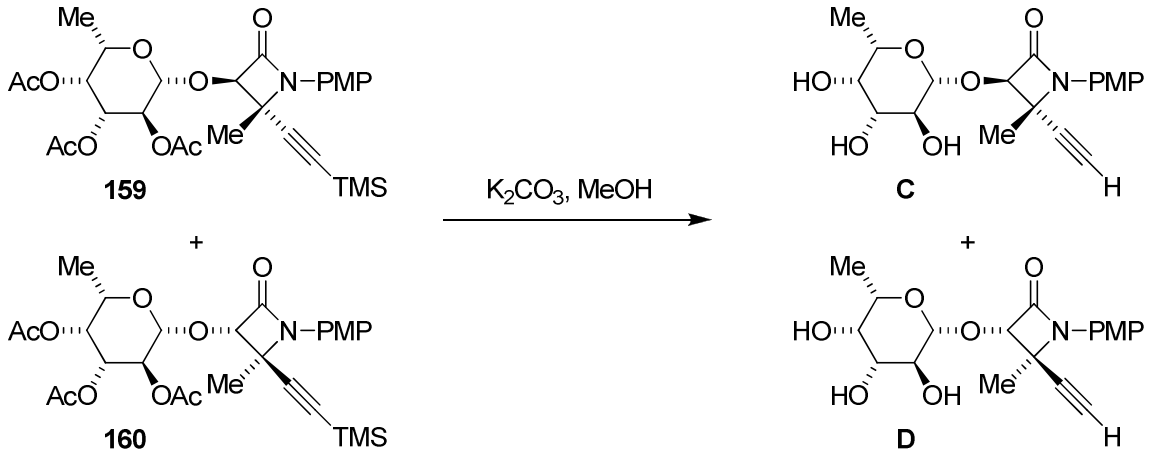
IR (neat) 2985, 2960, 2164, 1755, 1514, 1250, 1224, 1077, 846 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.8 Hz, 4 H), 6.87 (d, J = 9.2 Hz, 2 H), 6.86 (d, J = 9.2 Hz, 2 H), 5.27 (m, 4 H), 5.06 (m, 2 H), 5.05 (s, 1 H), 4.92 (s, 1 H), 4.83 (d, J = 8.0 Hz, 1 H), 4.68 (d, J = 8.0 Hz, 1 H), 3.89 (m, 2 H), 3.78 (s, 6 H), 2.19 (s, 3 H), 2.18 (s, 3 H), 2.06 (s, 6 H), 1.99 (s, 6 H), 1.65 (s, 3 H), 1.63 (s, 3 H), 1.26 (d, J = 6.4 Hz, 3 H), 1.25 (d, J = 6.8 Hz, 3 H), 0.17 (s, 9 H), 0.15 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.8, 170.7, 170.3, 170.2, 169.8, 169.3, 162.1, 161.6, 156.8, 129.8, 119.7, 119.6, 114.4, 106.9, 103.9, 103.7, 100.7, 100.5, 92.6, 92.2, 87.4, 87.3, 87.0, 84.3, 81.2, 76.4, 71.4, 71.2, 70.2, 70.0, 69.8, 68.8, 68.6, 58.3, 57.7, 55.6, 21.2, 21.0, 20.9, 20.8, 20.7, 20.7, 20.5, 20.4, 16.4, 16.2, 16.1, -0.2; HRMS calcd for $C_{28}H_{38}NO_{10}{}^{28}Si$ $[M+H]^+$: 576.2260, found: 576.2249.



β-lactam 159: In a dry 25 mL round bottomed flask under argon was added activated 4 Å molecular sieves (1.5 g) and (-)-2-hydroxy-3-(5-trimethylsilyl)alkynyl-3-methyl-*N*-(*p*-methoxyphenyl)-β-lactam **142** (292.4 mg,

0.979 mmol) with CH_2Cl_2 (3.8 mL). The reaction mixture was cooled to -15 °C (maintained at -15 °C (±5 °C) with dry-ice/acetone) and trichloroimidate **50** (prepared from 341 mg of 1-hydroxyl-2,3,4-triacetoxy-L-fucose) in CH_2Cl_2 (6.0 mL) was added. The mixture was stirred for 10 min, followed by addition of 2-3 drops of BF_3-THF. The reaction was stirred on cold bath for 3 h, then warmed to room temperature and stirred 5 h. The reaction was quenched with $NaHCO_3$ saturated solution (2 mL) under strong stirring. After 10 minutes, the reaction mixture was filtered through a pad of celite with ethyl acetate (25 mL), and solvent removed by vacuo. The crude reaction mixture was chromatographed (9:1 → 85:15 → 8:2 → 7:3, hexanes : ethyl acetate) to provide β-glycoside **159** (377.1 mg, 68%) as a sticky residue.

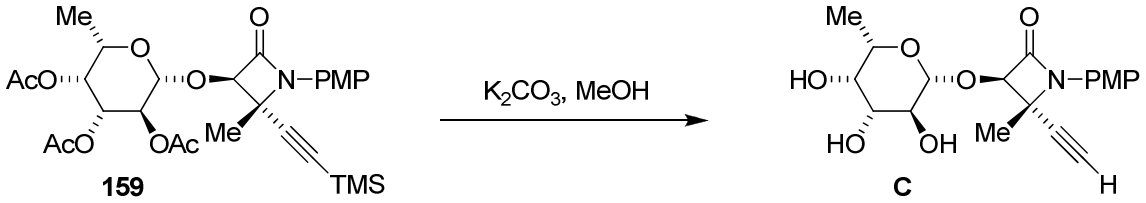
IR (neat) 2986, 2960, 2166, 1755, 1513, 1249, 1223, 1079, 846 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.57 (d, J = 9.2 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 5.26 (m, 2 H), 5.07 (q, J = 3.6, 1 H), 4.94 (s, 1 H), 4.84 (d, J = 8.0, 1 H), 3.91 (dq, J = 0.8, 6.8, 1 H), 3.80 (s, 3 H), 2.20 (s, 3 H), 2.07 (s, 3 H), 1.99 (s, 3 H), 1.66 (s, 3 H), 1.26 (d, J = 6.4, 3 H), 0.16 (s, 9 H); HRMS calcd for $C_{28}H_{38}NO_{10}{}^{28}Si$ $[M+H]^+$: 576.2260, found: 576.2259.



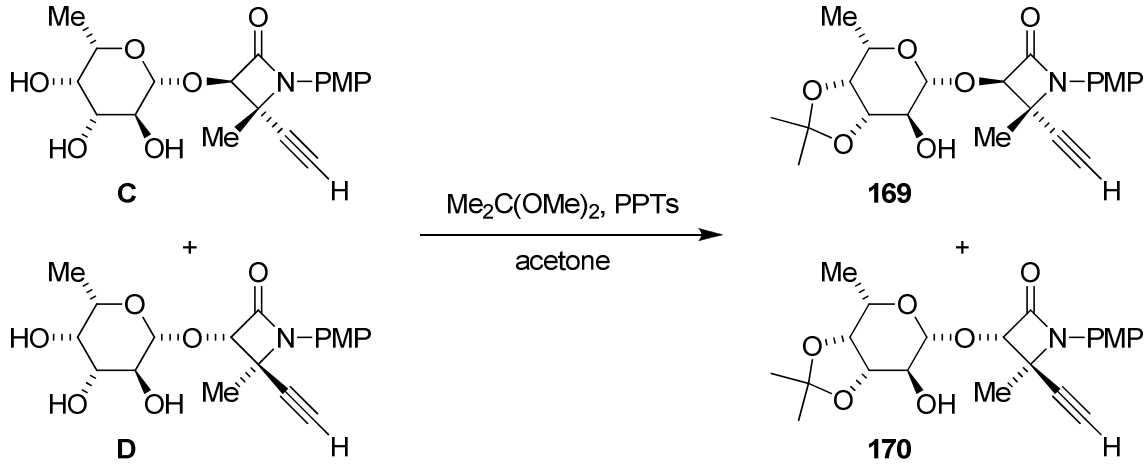
β-lactams C + D (as an inseparable mixture): A mixture of β-glycoside-β-lactam diastereomers **159** and **160** (12.69 g, 22.06 mmol) were taken up in MeOH (441 mL) at room temperature in a dry 1 L round bottomed flask under argon. Potassium carbonate (61.0 mg, 0.44 mmol) was added in one portion, and the reaction was stirred at ambient temperature overnight (10 h). Solvent was removed by vacuo, and the reaction chromatographed (98:2 → 95:5 → 9:1, $CHCl_3$: MeOH). 2,3,4-trihydroxy-β-glycoside-β-lactams **C** and **D** were isolated as a chromatographically inseparable mixture containing trace impurities (by ^1H NMR), as a sticky white solid (8.007 g product, 96%).

m.p.: 77-79 °C; IR (neat): 3393, 3297, 2984, 2936, 2113, 1746, 1514, 1250, 1082 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.58 (m, 4 H), 6.90 (d, J = 8.8 Hz, 4 H), 5.26 (s, 1 H), 4.97 (s, 1 H), 4.54 (d, J = 8.4 Hz, 1 H), 4.47 (d, J = 7.2, 1 H), 3.82 (m, 2 H), 3.81 (s, 6 H), 3.74 (m, 2 H), 3.67 (m, 2 H), 3.13 (m, 2 H), 2.70 (s, 1 H), 2.66 (s, 1 H), 1.78 (s, 3 H), 1.76 (s, 3 H), 1.40 (d, J = 6.4, 3 H), 1.39 (d, J = 6.8, 3 H); ^{13}C NMR (150 MHz, $CDC1_3$) δ 163.6, 163.2, 157.0, 129.4, 129.3, 119.9, 119.8, 114.6, 104.7, 102.0, 90.5, 89.1, 82.4, 75.9, 75.3, 74.0, 73.8, 71.7, 71.6, 71.4,

71.3, 70.3, 21.0, 20.5, 16.5; HRMS cald for $C_{19}H_{24}NO_7$ $[M+H]^+$: 378.1547, found: 378.1548.

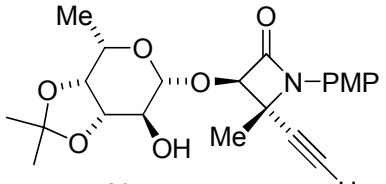


β-lactam C: β-glycoside-β-lactam **159** (371.9 mg, 0646 mmol) was taken up in MeOH (12.9 mL) at room temperature in a dry 25 mL round bottomed flask under argon. Potassium carbonate (1.8 mg, 0.01 mmol) was added in one portion, and the reaction was stirred at ambient temperature overnight (12 h). Solvent was removed by vacuo, and the reaction chromatographed using a gradient (95:5 → 9:1, $CHCl_3$: MeOH). Product was isolated as sticky white solid (some triethylamine from de-acidification of silica gel was retained by product) (236.9 g product, 97%).



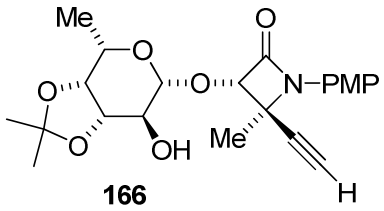
Acetonides 165 and 166 (separable): A mixture of β-glycosides **C** and **D** (8.01 g, 21.2 mmol) was taken up in acetone (212 mL, dried 3 h over 8-mesh white drierite) at room temperature under argon. To the solution was added pyridinium

p-toluenesulfonate (213 mg, 8.49 mmol) in one portion, followed by 2,2-dimethoxypropane (26.0 mL, 212 mmol). The reaction mixture was stirred at ambient temperature for 14 h, then quenched slowly with sodium bicarbonate saturated solution (100 mL), then poored into H_2O (50 mL) and ethyl acetate (100 mL) with stirring. After separation, the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The organic fractions were combined, dried over Na_2SO_4, and solvent removed by vacuo. Product diastereomers were then separated by column chromatography (7:3 → 6:4 → 1:1, hexanes : ethyl acetate) providing acetonide **165** (2.66 g, 30%) as a white solid, and acetonide **166** (3.28 g, 37%) as a white solid.



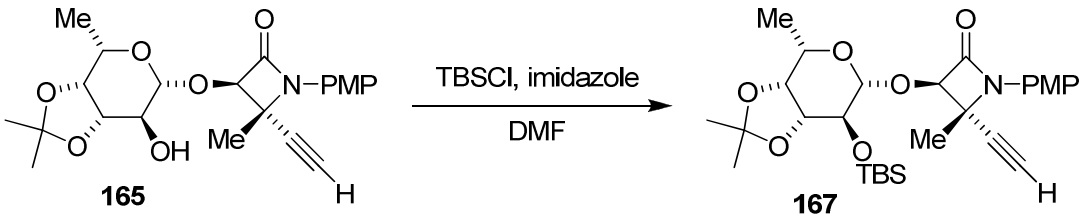
165

Acetonide 165 (2.66 g, 30%): m.p.: 158-159 °C; $[\alpha]_D$= -54 (*c* = 0.1, $CHCl_3$); IR (neat) 3449, 3267, 2987, 2936, 2875, 2114, 1749, 1513, 1248, 1083 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 4.95 (s, 1 H), 4.42 (d, J = 8.0 Hz, 1 H), 4.10 (dd, J = 5.6, 6.8 Hz, 1 H), 4.04 (d, J = 5.2 Hz, 1 H), 3.95 (q, J = 6.8 Hz, 1 H), 3.80 (s, 3 H), 3.63 (t, J = 7.6 Hz, 1 H), 2.67 (s, 1 H), 1.75 (s, 3 H), 1.55 (s, 3 H), 1.44 (d, J = 6.8 Hz, 3 H), 1.37 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5, 157.0, 129.5, 119.8, 114.6, 110.2, 103.7, 88.6, 82.6, 78.9, 76.4, 75.2, 73.7, 69.9, 58.4, 55.7, 28.4, 26.5, 20.9, 16.7; HRMS calcd for: $C_{22}H_{28}NO_7$ $[M+H]^+$: 418.1860, found: 418.1859.



166

Acetonide 166 (3.28 g, 37%): m.p.: 184-186 °C; $[\alpha]_D$= +27.1 (*c* 0.39, $CHCl_3$); IR (neat) 3474, 3270, 2987, 2936, 2874, 2122, 1754, 1513, 1382, 1248, 1081; ^1H (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.8 Hz, 2 H), 6.90 (d, J = 9.2 Hz, 2 H), 5.22 (s, 1 H), 4.44 (d, J = 8.8 Hz, 1 H), 4.09 (dd, J = 5.6, 7.6 Hz, 1 H), 4.04 (dd, J = 2.0, 5.6 Hz, 1 H), 3.97 (dd, J = 2.0, 6.4 Hz, 1 H), 3.81 (s, 3 H), 3.71 (dd, J =7.6, 8.0 Hz, 1 H), 3.25 (bs, 1 H), 2.70 (s, 1 H), 1.77 (s, 3 H), 1.56 (s, 3 H), 1.45 (d, J = 6.8, 3 H), 1.38 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0, 157.0, 129.3, 119.8, 114.6, 110.1, 100.9, 84.2, 82.4, 79.0, 76.5, 75.8, 72.9, 70.2, 57.3, 55.7, 28.5, 26.5, 20.5, 16.7; HRMS calcd for: $C_{22}H_{28}NO_7$ $[M+H]^+$: 418.860, found 418.1857.

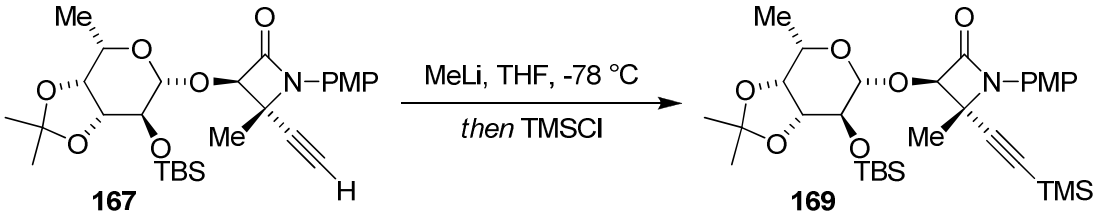


165 **167**

β-lactam glycoside 167: To a dry round bottomed flask, under argon, was added *t*-butyldimethylchlorosilane (2.89 g, 19.5 mmol) and imidazole (0.87 g, 12.8 mmol) in DMF (10 mL). Acetonide **165** (2.66 g, 6.38 mmol) in DMF (22 mL) was then added to the reaction mixture. The solution was stirred overnight (11 h) at ambient temperature, then poured into a stirring mixure of H_2O (50 mL) and ethyl acetate (75 mL). After separation, the organic layer washed with H_2O (2 × 15 mL). The organic fraction was dried over Na_2SO_4, solvent removed by vacuo,

and chromatographed (9:1, hexanes : ethyl acetate) to provide silylether **167** (3.31 g, 98%) as a white solid.

m.p.: 46-48 °C; $[\alpha]_D$ = -43.7 (*c* = 1.065, $CHCl_3$); IR (neat) 3292, 3263, 2987, 2933, 2856, 2114, 1760, 1514, 1249, 1139 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.59 (d, J = 9.6 Hz, 2 H), 6.80 (d, J = 9.2 Hz, 2 H), 4.94 (s, 1 H), 4.43 (d, J = 8.0 Hz, 1 H), 4.02 (m, 2 H), 3.91 (dq, J = 2.0, 6.8 Hz, 1 H), 3.80 (s, 3 H), 3.59 (dd, J = 6.4, 8.0 Hz, 1 H), 2.62 (s, 1 H), 1.75 (s, 3 H), 1.53 (s, 3 H), 1.42 (d, J = 6.4 Hz, 3 H), 1.37 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.3, 156.7, 129.8, 119.6, 114.5, 109.7, 103.4, 88.2, 82.8, 80.7, 76.7, 74.9, 74.3, 69.4, 58.0, 55.7, 28.3, 26.6, 26.0, 20.9, 18.4, 16.7, -4.3, -4.6; HRMS calcd for $C_{28}H_{42}NO_7{}^{28}Si$ $[M+H]^+$: 532.2735, found: 532.2723.

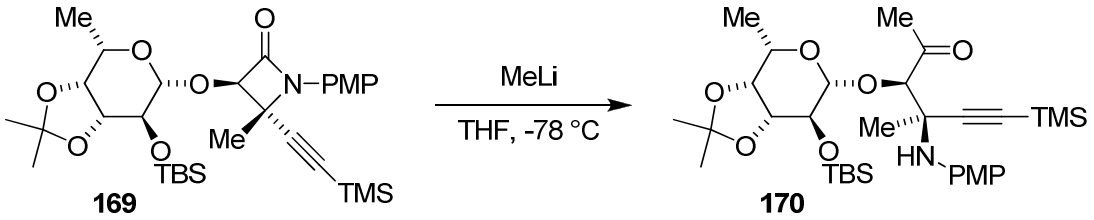


167 **169**

Fucoglycosidyl alkyne 169: In a dry 50 mL round bottomed flask under argon, alkyne **167** (3.31 g, 6.23 mmol) was added in THF (65 mL) and cooled to -78 °C (dryice/acetone bath). MeLi (1.6 M in Et_2O, 5.45 mL, 8.73 mmol) was added dropwise, and the reaction mixture was stirred for 1 hr. Chlorotrimethylsilane (1.42 mL, 11.2 mmol) was added dropwise, and the mixture stirred an additional hour at -78 °C. The reaction was quenched into a vigorously stirring solution of cold (ice-bath) saturated $NaHCO_3$ solution (75 mL) and ethyl acetate (75 mL). The fractions were separated and the aqueous phase extracted with additional ethyl acetate (2 × 75 mL). The organic fractions were combined, dried over

Na_2SO_4 and solvent removed by vacuo. Chromatography on silica gel (9:1, ethyl acetate : hexanes) provided TMS protected alkyne **169** as a white solid (3.27 g, 87%).

m.p.: 103 – 105 °C; $[\alpha]_D$ = -61.0 (*c* = 0.745, $CHCl_3$); IR (neat): 2987, 2856, 2165, 1762, 1513, 1381, 1249, 841 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.60 (d, J = 9.0 Hz, 1 H), 6.88 (d, J = 8.4, 1 H), 4.92 (s, 1 H), 4.46 (d, J = 7.6, 1 H), 4.02 (m, 2 H), 3.92 (dq, J = 2.0, 6.8, 1 H), 3.80 (s, 3 H), 3.58 (dd, J = 6.4, 7.6, 1 H), 1.70 (s, 3 H), 1.53 (s, 3 H), 1.43 (d, J = 6.4, 3 H), 1.37 (s, 3 H), 0.91 (s, 9 H), 0.17 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 156.6, 130.0, 119.6, 114.4, 109.7, 104.3, 103.2, 91.7, 88.0, 80.8, 76.7, 74.3, 69.4, 58.4, 55.6, 28.3, 26.7, 26.0, 21.0, 18.4, 16.7, -0.1, -4.3, -4.5; HRMS calcd for $C_{31}H_{50}NO_7{}^{28}Si_2$ $[M+H]^+$: 604.3120, found: 604.3110.

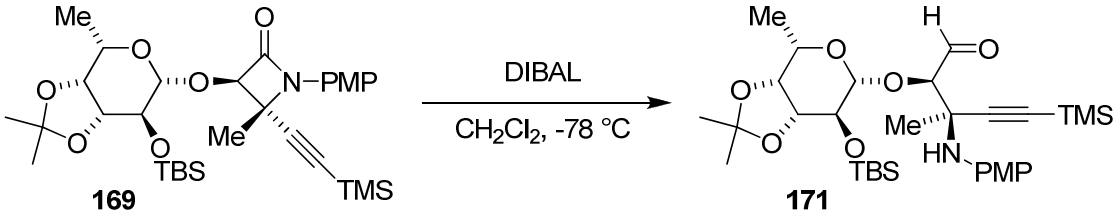


169 **170**

Ketone 170: Alkyne **169** (3.27 g, 5.41 mmol) was added to a dry round bottomed flask in THF (108 mL) under argon and was cooled to -78 °C. MeLi (1.6 M in Et_2O, 5.05 mL, 7.58 mmol) was then added dropwise over 10 minutes. The reaction was stirred for 1 h. then quenched into a vigorously stirring mixture of $NaHCO_3$ saturated solution (100 mL) / EtOAc (50 mL) which was cooled in advance in an icebath. The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 75 mL). The organic fractions were combined, dried over Na_2SO_4, filtered, and solvent removed by vacuo. Purification by column

chromatography (9:1, hexanes : ethyl acetate) provided **170** as a clear, sticky residue (3.56 mg, 97%).

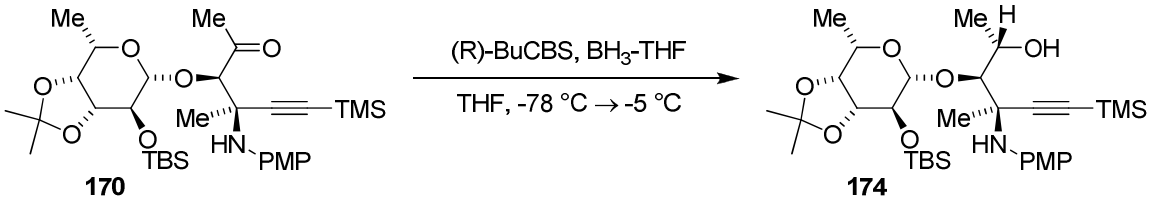
$[\alpha]_D$ = -19.0 (*c* = 0.515, $CHCl_3$); IR (neat): 3376, 2955, 2857, 2168, 1712, 1511, 1249, 1069, 864, 841 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.00 (d, J = 9.2 Hz, 2 H), 6.77 (d, J = 9.2 Hz, 2 H), 4.24 (s, 1 H), 4.19 (bs, 1 H), 4.14 (d, J = 7.6, 1 H), 4.00 (m, 2 H), 3.79 (dq, J = 1.6, 6.8 Hz, 1 H), 3.77 (s, 3 H), 3.65 (m, 1 H), 2.44 (s, 3 H), 1.54 (s, 3H), 1.47 (s, 3H), 1.39 (d, J = 6.8 Hz, 3 H), 1.35 (s, 3H), 0.94 (s, 9 H), 0.21 (s, 3H), 0.20 (s, 3 H), 0.12 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 154.5, 138.6, 122.4, 114.0, 109.8, 106.2, 101.1, 91.9, 86.9, 80.7, 76.6, 74.4, 69.5, 55.8, 54.9, 29.0, 28.2, 26.5, 26.2, 25.4, 18.3, 16.6, -0.1, -3.4, -4.0; HRMS calcd for $C_{32}H_{54}NO_7{}^{28}Si_2$ $[M+H]^+$: 620.3433, found: 620.3434.



Aldehyde 171: Alkyne **169** (61.7 mg, 0.102 mmol) was added to a dry 10 mL round bottomed flask with CH_2Cl_2 (4.0 mL) under argon and cooled to -78 °C. DIBAL (1.0 M in hexanes, 0.11 mL, 0.107 mmol) was added dropwise over 3 min. The reaction was stirred for 2 h, then quenched cold with saturated Rochelle's salt solution (5 mL), stirring vigorously for 3 hours while warming slowly to room temperature. Extraction was carried out using additional H_2O (10 mL) and EtOAc (10 mL). The aqueous phase was extracted with additional ethyl acetate (2 × 10 mL), the organic fractions were combined, dried over Na_2SO_4, and solvent removed by *vacuo*. The reaction mixture was chromatographed (85 :

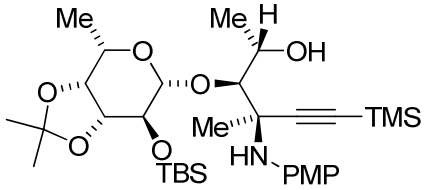
15, hexanes : ethyl acetate) providing aldehyde **171** as a clear residue (61.5 mg, 99%).

$[\alpha]_D$ = -34 (*c* = 0.185, $CHCl_3$); IR (neat) 3373, 2929, 2856, 2168, 1735, 1511, 1249, 1068, 841 cm^{-1}; ^1H (600 MHz, $CDCl_3$) δ 9.92 (d, J = 2.4 Hz, 1 H), 7.02 (d, J = 9.0 Hz, 2 H), 6.78 (d, J = 9.0 Hz, 2 H), 4.32 (d, J = 7.8 Hz, 1 H), 4.09 (d, J = 3.0 Hz, 1 H), 4.02 (dd, J = 6.0, 6.0 Hz, 1 H), 4.00 (dd, J = 1.8, 5.4 Hz, 1 H), 3.82 (dq, J = 1.8, 6.6 Hz, 1 H), 3.78 (s, 3 H), 3.63 (dd, J = 6.6, 7.8 Hz, 1 H), 1.58 (s, 3 H), 1.54 (s, 3 H), 1.52 (s, 3 H), 1.40 (d, J = 7.2 Hz, 3 H), 1.36 (s, 3 H), 0.94 (s, 9 H), 0.19 (s, 3 H), 0.18 (s, 3 H), 0.15 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.4, 154.5, 138.4, 121.8, 114.2, 109.8, 105.5, 101.6, 92.4, 84.7, 80.6, 76.6, 74.2, 69.3, 55.8, 54.8, 28.3, 26.6, 26.1, 26.0, 24.6, 18.4, 16.7, -0.1, -3.9, -4.2; HRMS calcd for $C_{32}H_{52}NO_7{}^{28}Si_2$ $[M+H]^+$: 606.3277, found: 606.3272.



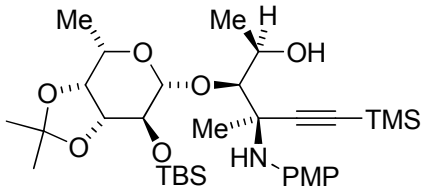
Secondary Alcohol 174: In a dry round bottomed flask was charged ketone **170** (3.258 mg, 5.255 mmol) in THF (105 mL) under argon and cooled to -78 °C (dry-ice/acetone bath). (R)-Bu-CBS solution (0.05 M in toluene, 68.3 mL, 3.42 mmol) was added dropwise, the reaction was stirred for 20 minutes. BH_3-THF solution (1.0 M in THF, 110 mL, 11.0 mmol) was then added dropwise over 3 minutes. The solution was allowed to warm slowly to -5 °C over 3 h, and then stirred at -5 °C for an additional 4 h. The reaction mixture was quenched into a

cold (icebath) mixture of $NaHCO_3$ saturated solution (50 mL) and EtOAc (50 mL) with vigorous stirring. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 50 mL), the organic fractions combined, dried over Na_2SO_4, and solvent removed by *vacuo*. Column chromatorgraphy (9 : 1 → 85 : 15 → 7 : 3, hexanes : ethyl acetate) separately provided secondary alcohols **174** (2.649 g, 81%) and **175** (166 mg slightly crude, ~5%), (>15 : 1, **174** : **175** by ^1H NMR), each as a sticky residue. Alcohol **174** readily isomerized upon standing to a mixture of silyl-migratory isomers (see **216**).



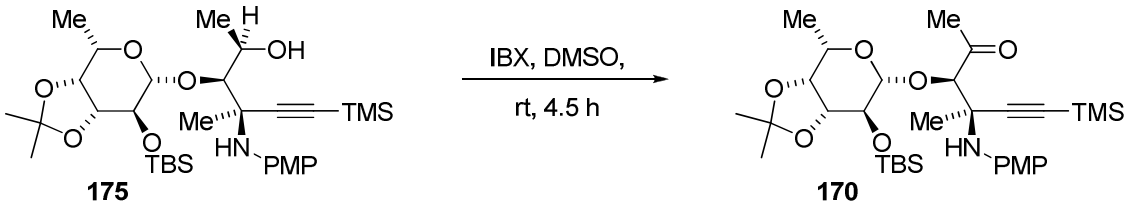
174

Secondary alcohol 174: $[\alpha]_D$ = -73 (*c* = 0.195 , $CHCl_3$); IR (neat) 3360, 2928, 2856, 2166, 1511, 1249, 1068, 1039, 865, 840 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.8 Hz, 2 H), 6.77 (d, J = 9.2 Hz, 2 H), 4.45 (d, J = 7.6 Hz, 1 H), 4.28 (dq, J = 4.8, 6.8 Hz, 1 H), 4.01 (m, 2 H), 3.88 (q, J = 6.8 Hz, 1 H), 3.77 (s, 3 H), 3.73 (d, J = 4.8 Hz, 1 H), 3.62 (m, 1 H), 1.54 (s, 3 H), 1.49 (s, 3 H), 1.45 (d, J = 6.8 Hz, 3 H), 1.42 (d, J = 6.8 Hz, 3 H), 1.35 (s, 3 H), 0.95 (s, 9 H), 0.19 (s, 3 H), 0.18 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 139.0, 121.6, 114.1, 109.6, 107.4, 103.6, 91.5, 86.9, 81.0, 76.8, 75.3, 69.9, 69.1, 55.8, 55.6, 28.3, 26.5, 26.3, 25.1, 19.8, 18.5, 16.7, -0.1, -3.6, -3.8; HRMS calcd for $C_{32}H_{56}NO_7{}^{28}Si_2$ $[M+H]^+$: 622.3590, found: 622.3588.



175

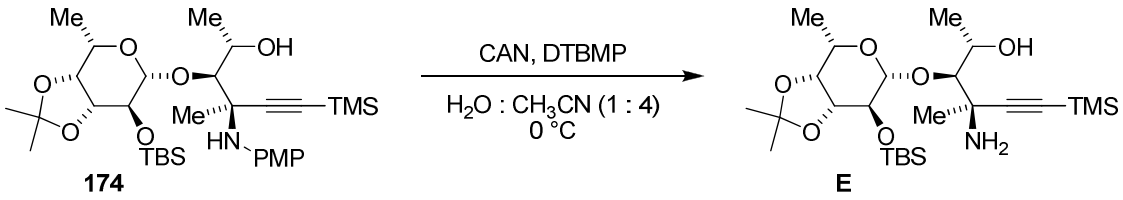
Secondary alcohol 175: $[\alpha]_D$ = -84 (*c* = 0.120, $CHCl_3$); IR (neat) 3369, 2926, 2855, 2170, 1511, 1249, 1069, 1039, 841 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 9.2 Hz, 2 H), 4.50 (dq, J = 4.4, 6.0 Hz, 1 H), 4.45 (d, J = 7.6, 1 H), 4.03 (q, J = 5.6 Hz, 1 H), 4.01 (m, 1 H), 3.86 (dq, J = 2.0, 6.4 Hz, 1 H), 3.78 (s, 3 H), 3.61 (dd, J = 5.6, 7.6 Hz, 1 H), 3.48 (d, J = 4.4 Hz, 1 H), 1.55 (s, 3 H), 1.52 (s, 3 H), 1.41 (d, J = 6.4, 3 H), 1.37 (d, J = 6.8 Hz, 3 H), 1.36 (s, 3 H), 0.94 (s, 9 H), 0.21 (s, 3 H), 0.19 (s, 3 H), 0.15 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.4, 138.5, 122.0, 114.0, 109.6, 107.2, 103.4, 91.7, 86.2, 80.8, 76.8, 75.1, 69.6, 68.3, 57.1, 55.8, 28.4, 26.5, 26.2, 26.1, 21.3, 18.4, 16.7, -0.1, -3.7, -4.2; HRMS calcd for $C_{32}H_{56}NO_7{}^{28}Si_2$ $[M+H]^+$: 622.3590, found: 622.3587.



175 **170**

Oxidation of 175 to Ketone 170: In a dry 10 mL round bottomed flask was added **175** (42.1 mg, 0.068 mmol) in DMSO (4.0 mL), then added IBX (55.3 mg, 0.197 mmol) and the reaction mixture stirred at ambient temperature. After 4.5 h the reaction appeared complete by TLC. The reaction mixture was quenched into cold (ice bath) $NaHCO_3$ saturated solution (35 mL) and EtOAc (35 mL) under strong stirring. The layers were separated, and the aqueous phase extracted

with EtOAc (2 × 35 mL). The organic fractions were combined, dried over Na_2SO_4, and removed solvent under reduced pressure. The crude mixture was then chromatographed (9:1 → 85:15, hexanes : EtOAc) to provide ketone **170** (39.7 mg, **95%**).

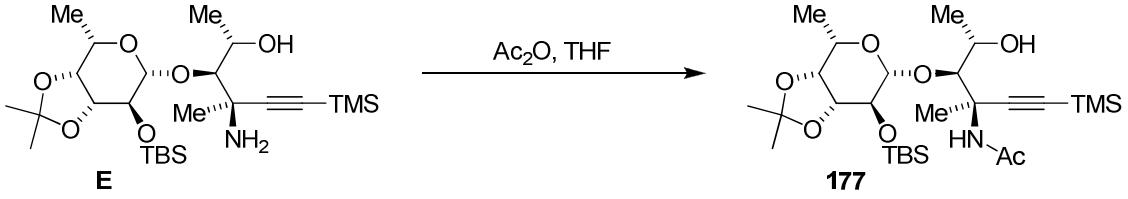


174 **E**

Amine E: Secondary alcohol **174** (99.3 mg, 0.160 mmol) was transfered with acetonitrile (4.3 mL) to a round bottomed flask containing 2,6-di-*tert*-butyl-4-methylpyridine (101.6 mg, 0.495 mmol) and cooled to 0 °C (icebath). Ammonium cerium nitrate (262.6 mg, 0.479 mmol) was taken up in H_2O (de-ionized, 1.1 mL) and added to the cold acetonitrile solution dropwise. (COLOR CHANGE: the reaction will turn darker with each additional drop of CAN solution, and will turn dark-brown – black over the course of the reaction). The solution was stirred for 6 h at 0 °C (icebath), then quenched into a cold (icebath) stirring mixture of $NaHCO_3$ saturated solution (25 mL) and ethyl acetate (25 mL). The phases were separated, and the aqueous layer extracted with additional ethyl acetate (2 × 20 mL), the organic fractions combined, dried over Na_2SO_4, and solvent removed by *vacuo*. Chromatrography (8:2 → 9:1, → 1:0, ethyl acetate : hexanes) provided primary amine **E** (71.0 mg, 86%) as a residue.

$[\alpha]_D$ = -4.3 (*c* = 2.70, $CHCl_3$); IR (neat) 3366, 3293, 2933, 2858, 2167, 1380, 1250, 1072, 866, 841 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 4.37 (d, J = 8.0 Hz, 1 H), 4.04 (dq, J = 5.2, 6.4 Hz, 1 H), 3.98 (m, 2 H), 3.82 (dq, J = 1.6, 6.4 Hz, 1 H), 3.59 (m,

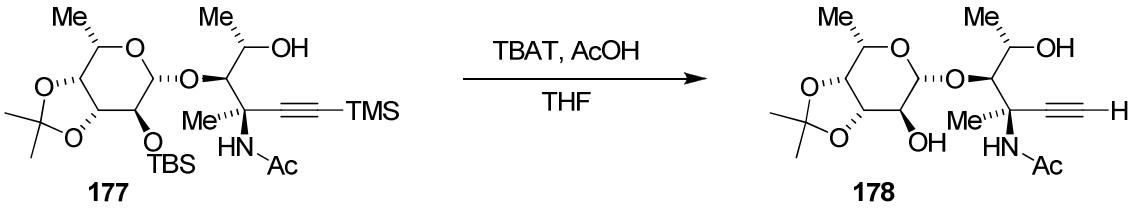
1 H), 3.51 (d, J = 5.2 Hz, 1 H), 1.53 (s, 3 H), 1.40 (s, 3 H), 1.38 (d, J = 6.4 Hz, 6 H), 1.34 (s, 3 H), 0.93 (s, 9 H), 0.17 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 110.9, 109.9, 103.9, 88.0, 87.0, 81.4, 77.2, 75.7, 69.9, 69.4, 51.5, 28.8, 28.6, 26.8, 26.6, 20.2, 18.8, 17.0, 0.4, -3.4, -3.5; HRMS calcd for $C_{25}H_{50}NO_6{}^{28}Si_2$ $[M+H]^+$: 516.3171, found: 516.3167.



E **177**

Acetamide 177: Primary amine **E** (47.6 mg, 0.092 mmol) was taken up in THF (4.6 mL) in a dry 10 mL round bottomed flask under argon, and acetic anhydride (0.01 mL, 0.102 mmol) was added. The reaction was stirred for 5 h at ambient temperature. The solvent was then removed by *vacuo* and crude material chromatographed (6:4, hexanes : ethyl acetate) to provide acetamide **177** (49.6 mg, 96%) as a white solid.

m.p.: 58 °C – 60 °C; $[\alpha]_D$ = -99 (*c* = 0.105, $CHCl_3$); IR (neat) 3354, 2934, 2858, 2173, 1671, 1250, 1069, 1039, 867, 841 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 6.88 (s, 1 H), 4.41 (d, J = 7.6 Hz, 1 H), 4.05 (dq, J = 4.4, 6.8 Hz, 1 H), 3.99 (m, 2 H), 3.89 (dq, J = 1.6, 6.8 Hz, 1 H), 3.61 (m, 2 H), 2.84 (d, J = 8.0 Hz, 1 H), 1.94 (s, 3 H), 1.69 (s, 3 H), 1.53 (s, 3 H), 1.40 (d, J = 6.4 Hz, 3 H), 1.33 (s, 3 H), 0.92 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 109.7, 105.1, 104.0, 88.7, 86.8, 80.8, 76.6, 75.1, 69.7, 68.6, 52.8, 28.3, 26.4, 26.3, 24.9, 24.6, 19.5, 18.4, 16.9, 0.07, -3.56, -3.78; HRMS calcd for $C_{27}H_{52}NO_7{}^{28}Si_2$ $[M+H]^+$: 558.3277, found: 558.3267.

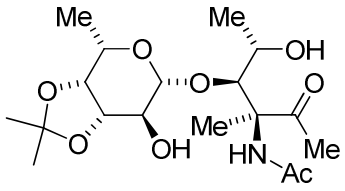


177 178

Alkyn alcohol 178: In a dry 10 mL round bottomed flask was added tetrabutylammonium triphenyldifluorosilicate (97%, 445.0 mg, 0.824 mmol) and alkyne **177** (46.0 mg, 0.082 mmol) in THF (2.7 mL) at 0 °C (ice-bath) under argon, followed immediately by addition of acetic acid (0.05 mL, 0.82 mmol). The reaction was warmed slowly to room temperature over 1 h. Reaction proceeds, and begins to slow over time. After 5 d, more tetrabutylammonium triphenyldifluorosilicate (97%, 100.0 mg, 0.185 mmol) along with acetic acid (0.01 mL, 0.18 mmol) and stirred 2 d (7 days total). The reaction was then poured into cold (ice-bath) ammonium chloride saturated solution (20 mL) and ethyl acetate (20 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (2 × 20 mL), the organic fractions combined, dried over Na_2SO_4, and solvent removed by vacuo. Column chromatorgraphy (9:1 → 1:0, ethyl acetate : hexanes) provided alkynol **177** (25.9 mg, 85%) as a while solid.

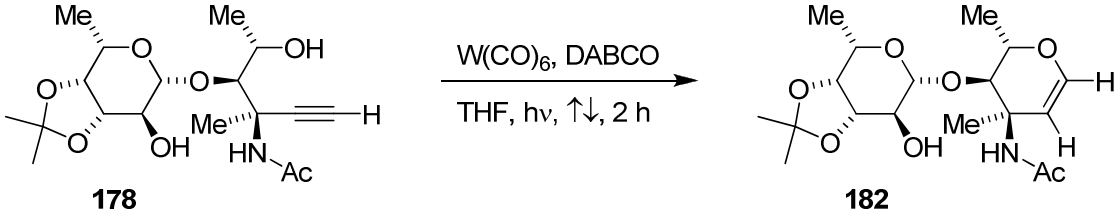
m.p. = 194 °C – 195 °C; $[\alpha]_D$ = -109 (*c* = 0.140, $CHCl_3$); IR (neat) 3341, 2987, 2936, 2115, 1667, 1539, 1374, 1068, 1035, 736 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.87 (bs, 1 H), 4.47 (d, J = 8.4 Hz, 1 H), 4.14 (dq, J = 2.8, 6.8 Hz, 1 H), 4.08 (dd, J = 5.2, 6.8 Hz, 1 H), 4.02 (dd, J = 2.4, 5.6 Hz, 1 H), 3.96 (dq, J = 2.4, 6.8 Hz, 1 H), 3.75 (d, J = 3.2 Hz, 1 H), 3.71 (dd, J = 7.6, 8.0 Hz, 1 H), 3.16 (bs, 2 H), 2.43 (s, 1 H), 1.98 (s, 3 H), 1.75 (s, 3 H), 1.57 (s, 3 H), 1.46 (d, J = 6.8 Hz, 3 H), 1.44 (d, J = 6.4 Hz, 3 H), 1.38 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 110.4,

104.7, 89.1, 83.3, 79.8, 76.4, 74.1, 73.1, 69.8, 68.2, 52.3, 28.4, 26.5, 24.6, 24.3, 18.5, 17.0; HRMS calcd for $C_{18}H_{29}LiNO_7$ $[M+Li]^+$: 378.2099, found: 378.2093, calcd for $C_{18}H_{29}NNaO_7$ $[M+Na]^+$: 394.1836, found: 394.1835.



180

Ketone side product 180: m.p. = 177 °C – 179 °C; $[\alpha]_D$ = -51 (*c* = 0.305, $CHCl_3$); IR (neat) 3453, 2983, 2934, 1712, 1669, 1381, 1221, 1071, 1041 cm^{-1}; 4.20 (d, J = 8.4 Hz, 1 H), 4.14 (d, J = 9.2 Hz, 1 H), 4.03 (m, 2 H), 3.95 (dd, J = 2.4, 5.6 Hz, 1 H), 3.70 (dq, J = 2.4, 6.4 Hz, 1 H), 3.48 (dd, J = 7.2, 8.0 Hz, 1 H), 2.31 (s, 3 H), 1.91 (s, 3 H), 1.52 (s, 3 H), 1.45 (s, 3 H), 1.37 (d, J = 6.0 Hz, 3 H), 1.34 (s, 3 H), 1.30 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 156.6, 110.0, 103.3, 79.1, 77.4, 76.6, 73.8, 69.4, 69.2, 65.3, 28.5, 26.5, 25.6, 21.5, 21.4, 18.6, 16.6; HRMS calcd for $C_{18}H_{32}NO_8$ $[M+H]^+$: 390.2122, found: 390.2124.

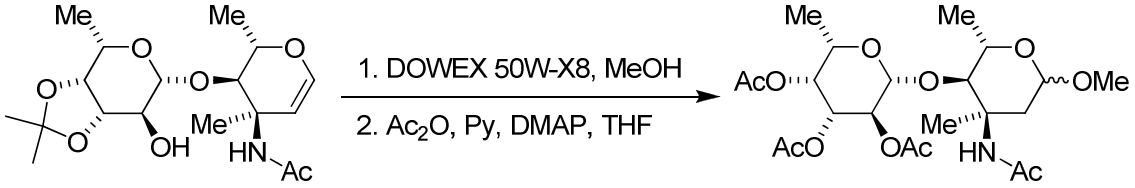


178 **182**

Saccharosamine glycal 182: Alkynol **178** (21.2 mg, 0.057 mmol) was added in THF (2.0 mL) in a dry 5-mL round bottomed flask containing 1,4-diazabicyclo[2.2.2]octane (12.8 mg, 0.114 mmol) and tungsten hexacarbonyl (5.1 mg, 0.014 mmol) under argon. A reflux condenser was fixed to the flask, and the

reaction mixture was exposed to hν (350 nm, Rayonet Photoreactor) and allowing the reaction to warm to 60 ℃. The reaction was stirred for 2 hours, then filtered through a short plug of celite with ethyl acetate, and chromatorgraphed (85:15 → 1:0, EtOAc : Hexanes) to provide glycal **182** as a white solid (20.2 mg, 95%).

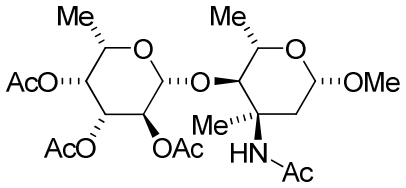
m.p. = 73 °C – 75 °C; $[\alpha]_D$ = -143 (*c* = 0.170, $CHCl_3$); IR (neat) 3404, 2984, 2934, 2854, 1749, 1678, 1513, 1370, 1222, 1070 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.20 (d, J = 6.4 Hz, 1 H), 6.09 (s, 1 H), 5.44 (d, J = 6.0 Hz, 1 H), 4.30 (d, J = 8.0 Hz, 1 H), 4.06 (dd, J = 6.0, 7.2 Hz, 1 H), 4.02 (dd, J = 2.0, 5.6 Hz, 1 H), 3.98 (dq, J = 6.4, 10.2 Hz, 1 H), 3.87 (dq, J = 2.4, 6.4 Hz, 1 H), 3.59 (dd, J = 7.2, 8.0 Hz, 1 H), 3.37 (d, J = 10.4 Hz, 1 H), 2.86 (bs, 1 H), 1.93 (s, 3 H), 1.56 (s, 3 H), 1.49 (s, 3 H), 1.42 (d, J = 6.0 Hz, 3 H), 1.38 (d, J = 6.0 Hz, 3 H), 1.37 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 141.8, 110.2, 106.0, 103.1, 84.1, 79.5, 76.4, 74.0, 70.6, 69.6, 52.5, 28.4, 26.4, 24.8, 24.6, 17.8, 16.6; HRMS calcd for $C_{18}H_{29}NO_7$ $[M+H]^+$: 372.2017, found: 372.2020.



182 **135 + 184**

Disaccharides 135 and 184: Glycal **182** (20.2 mg, 0.054 mmol) was taken up in methanol (5.4 mL) at room temperature with DOWEX 50W-X8 (40.4 mg). The reaction was stirred at ambient temperature for 7.5 h, then filtered through a short plug of celite with MeOH (20 mL). Solvent was removed by *vacuo* and cleavage of acetonide, along with installation of anomeric methoxy group, was

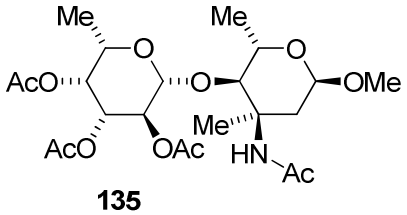
confirmed by ^{1}H NMR. Crude material was then transferred to a dry 10 mL round bottomed flask with methanol, solvent removed by *vacuo* and dried under high vacuum for 2 h. THF (5.4 mL) was added (NOTE: intermediate triol is not soluble in THF) followed by acetic anhydride (0.03 mL, 0.297 mmol) and pyridine (0.01 mL, 0.18 mmol). The reaction was stirred at ambient temperature for 2 h with no reaction, at which point DMAP (99%, 0.07 mg, 0.005 mmol) was added, along with more acetic anhydride (0.03 mL, 0.297 mmol), and the mixture stirred for 5 h. The reaction was quenched into cold (icebath) $NaHCO_3$ saturated solution (40 mL) and ethyl acetate (40 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 40 mL). The organic fractions were combined, dried over Na_2SO_4, solvent removed by *vacuo*, and chromatographed (65:35 → 7:3, ethyl acetate : hexanes) to provide final disaccharide product in 63% yield over two steps as a separable mixture of saccharosamine anomers **184** (12.1 mg, 45%) and **135** (4.2 mg, 18%).



184

Dissaccharide 184: m.p. = 202 °C – 203 °C; $[\alpha]_D$ = +11.7 (*c* = 0.395, $CHCl_3$); IR (neat) 3404, 2984, 2934, 2854, 1749, 1678, 1513, 1370, 1222, 1070 cm^{-1}; ^{1}H (400 MHz, $(CD_3)_2SO$) δ 6.32 (s, 1 H), 5.14 (dd, J = 3.6, 10.0 Hz, 1 H), 5.10 (dd, J = 3.6, 0.8 Hz, 1 H), 4.92 (dd, J = 8.0, 10.4 Hz, 1 H), 4.80 (d, J = 8.4 Hz, 1 H), 4.33 (dd, J = 1.6, 9.6 Hz, 1 H), 4.03 (q, J = 6.4 Hz, 1 H), 3.73 (dq, J = 6.4, 9.6 Hz, 1 H), 3.28 (s, 3 H), 3.09 (d, J = 9.6 Hz, 1 H), 3.07 (m, 1 H), 2.14 (s, 3 H), 2.04 (s,

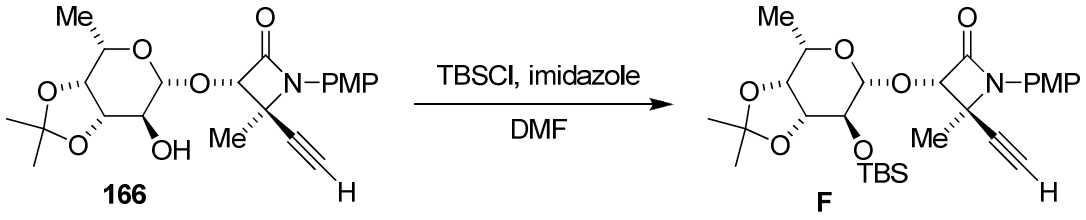
3 H), 1.92 (s, 3 H), 1.85 (s, 3 H), 1.35 (s, 3 H), 1.22 (d, J = 6.4 Hz, 3 H), 1.15 (m, 1 H), 1.05 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ 170.2, 169.5, 169.4, 169.3, 100.2, 98.8, 84.9, 70.7, 70.1, 69.3, 68.6, 68.1, 55.4, 55.2, 38.6, 24.1, 24.0, 20.7, 20.5, 20.4, 17.9, 15.5; HRMS calcd for $C_{22}H_{36}NO_{11}$ $[M+H]^+$: 490.2283, found: 490.2280.



135

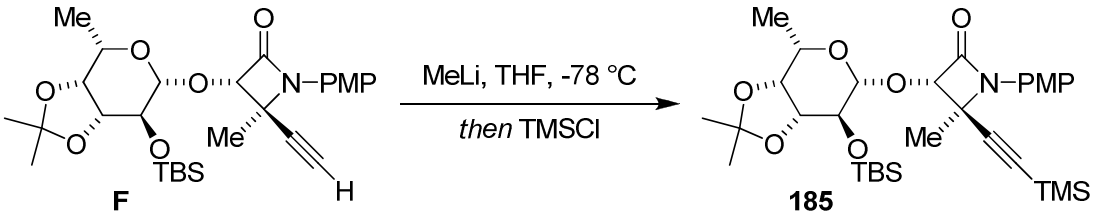
Dissaccharide 135: m.p. = 173 °C – 175 °C; $[\alpha]_D$ = -52 (*c* = 0.18, $CHCl_3$); IR (neat) 3424, 2987, 2934, 1750, 1671, 1369, 1221, 1066, 755 cm^{-1}; ^{1}H (400 MHz, $(CD_3)_2SO$) δ 6.43 (s, 1 H), 5.12 (m, 2 H), 4.92 (dd, J = 8.4, 10.0 Hz, 1 H), 4.80 (d, J = 8.0 Hz, 1 H), 4.50 (dd, J = 1.6, 4.4 Hz, 1 H), 4.04 (q, J = 6.8 Hz, 1 H), 3.85 (dq, J = 6.4, 9.2 Hz, 1 H), 3.15 (s, 3 H), 3.14 (d, J = 9.6 Hz, 1 H), 2.88 (dd, J = 1.6, 14.4 Hz, 1 H), 2.14 (s, 3 H), 2.04 (s, 3 H), 1.92 (s, 3 H), 1.75 (s, 3 H), 1.53 (dd, J = 4.4, 14.8 Hz, 1 H), 1.36 (s, 3 H), 1.20 (d, J = 6.4 Hz, 3 H), 1.05 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ 170.3, 169.5, 169.2, 169.0 100.4, 97.4, 85.1, 70.7, 69.2, 68.1, 63.3, 54.5, 53.1, 35.4, 24.6, 24.2, 20.7, 20.4, 17.7, 15.5; HRMS calcd for $C_{22}H_{36}NO_{11}$ $[M+H]^+$: 490.2283, found: 490.2279.

3.1.2. Experimental procedures of section 2.2



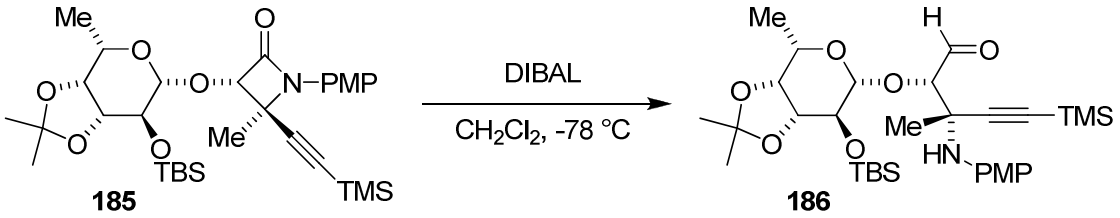
β-lactam glycoside F: To a dry round bottomed flask, under argon, was added *t*-butyldimethylchlorosilane (3.37 g, 22.3 mmol) and imidazole (1.01 g, 14.9 mmol) in DMF (20 mL). Acetonide **166** (3.11 g, 7.44 mmol) in DMF (17 mL) was then added to the reaction mixture. The solution was stirred overnight (12 h) at ambient temperature, then poured into a stirring mixure of H_2O (100 mL) and ethyl acetate (100 mL). After separation, the organic layer washed with H_2O (2 × 50 mL). The organic fraction was dried over Na_2SO_4, solvent removed by vacuo, and chromatographed (9:1, hexanes : ethyl acetate) to provide silylether **F** (3.73 g, 94%) as a white solid.

m.p.: 40 – 42 °C; $[\alpha]_D$ = +32.8 (*c* = 0.385, $CHCl_3$); IR (neat): 3265, 2986, 2934, 2857, 2116, 1761, 1513, 1249, 1136, 1093, 837 cm^{-1}; ^1H (600 MHz, $CDCl_3$) δ 7.58 (d, J = 9.0 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 5.17 (s, 1 H), 4.44 (d, J = 7.8 Hz, 1 H), 4.02 (m, 2 H), 3.92 (q, J = 6.6 Hz, 1 H), 3.80 (s, 3 H), 3.65 (dd, J = 6.0, 7.2 Hz, 1 H), 2.66 (s, 1 H), 1.77 (s, 3 H), 1.53 (s, 3 H), 1.42 (d, J = 6.6 Hz, 3 H), 1.35 (s, 3 H), 0.90 (s, 9 H), 0.15 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.1, 156.8, 129.7, 119.6, 114.6, 109.8, 101.5, 86.0, 82.8, 80.8, 76.6, 75.4, 74.1, 69.6, 56.9, 55.7, 28.2, 26.5, 26.1, 20.8, 18.3, 16.7, -4.2, -4.2; HRMS calcd for $C_{28}H_{42}NO_7{}^{28}Si$ $[M+H]^+$: 532.2735, found: 532.2721.



F **185**

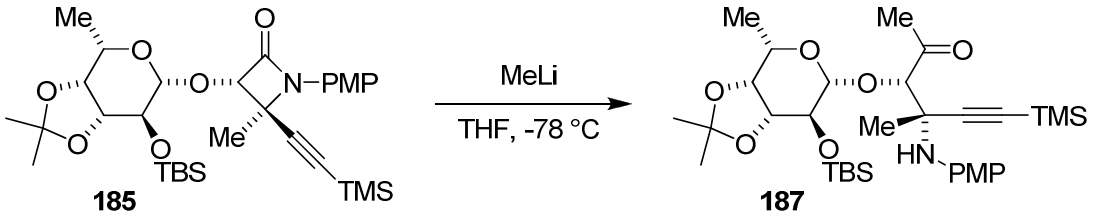
β-lactam 185: In a dry 50 mL round bottomed flask under argon, alkyne **F** (1.686 g, 3.171 mmol) was added in THF (32.0 mL) and cooled to -78 °C (dryice/acetone bath). MeLi (1.6 M in Et_2O, 2.18 mL, 3.49 mmol) was added dropwise, and the reaction mixture was stirred for 1 hr. Chlorotrimethylsilane (0.81 mL, 6.34 mmol) was added dropwise, and the mixture stirred an additional 1.5 hours. The reaction was quenched into a vigorously stirring solution of cold (ice-bath) saturated $NaHCO_3$ solution (50 mL) and ethyl acetate (50 mL). The fractions were separated and the aqueous phase extracted with additional ethyl acetate (2 × 50 mL). The organic fractions were combined, dried over Na_2SO_4 and solvent removed by vacuo. Chromatography on silica gel (9:1, ethyl acetate : hexanes) provided TMS protected alkyne **185** as a white solid (1.766 mg, 92%). m.p. = 38 °C – 40 °C; $[\alpha]_D$ = +58, (*c* = 0.160, $CHCl_3$); IR (neat) 2956, 2858, 2166, 1762, 1513, 1380, 1248, 841 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.59 (d, J = 9.6 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 5.11 (s, 1 H), 4.45 (d, J = 7.6 Hz, 1 H), 4.02 (m, 2 H), 3.92 (dq, J = 1.6, 6.8 Hz, 1 H), 3.81 (s, 3 H), 3.65 (dd, J = 6.0, 8.0 Hz, 1 H), 1.73 (s, 3 H), 1.53 (s, 3 H), 1.43 (d, J = 6.4 Hz, 3 H), 1.36 (s, 3 H), 0.91 (s, 9 H), 0.17 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 156.6, 129.9, 119.5, 114.4, 109.7, 104.3, 101.6, 92.2, 86.4, 80.8, 76.6, 74.2, 69.6, 57.3, 55.6, 28.2, 26.6, 26.1, 20.8, 18.3, 16.7, -0.1, -4.2, -4.3; HRMS calcd for $C_{31}H_{50}NO_7{}^{28}Si_2$ $[M+]^+$: 604.3120, found: 604.3111.



185 **186**

Aldehyde 186: β-lactam **185** (25.5 mg, 0.042 mmol) was added to a dry 10 mL round bottomed flask with CH_2Cl_2 (4.0 mL) under argon and cooled to -78 °C. DIBAL (1.0 M in hexanes, 0.05 mL, 0.46 mmol) was added dropwise over 3 min. The reaction was stirred for 2 h, then quenched cold with saturated Rochelle's salt solution (4.0 mL), stirring vigorously for 3 hours while warming slowly to room temperature. Extraction was carried out using additional H_2O (15 mL) and EtOAc (15 mL). The aqueous phase was extracted with additional ethyl acetate (2×15 mL), the organic fractions were combined, dried over Na_2SO_4, and solvent removed by *vacuo*. The reaction mixture was chromatographed (9 : 1, hexanes : ethyl acetate) providing aldehyde **186** as a clear residue (25.5 mg, >99%).

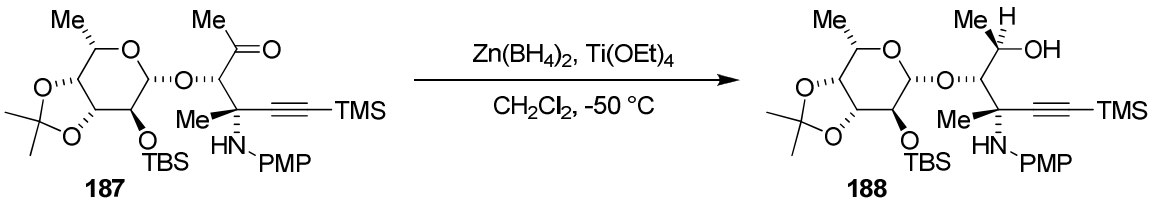
$[\alpha]_D$ = +10 (*c* = 0.270, $CHCl_3$); IR (neat) 3359, 2932, 2857, 2165, 1735, 1510, 1249, 1077, 841 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 9.61 (d, J = 3.6 Hz, 1 H), 7.06 (d, J = 8.4 Hz, 2 H), 6.78 (d, J = 8.4 Hz, 2 H), 4.33 (d, J = 7.8 Hz, 1 H), 4.02 (m, 2 H), 3.81 (m, 1 H), 3.79 (s, 3 H), 3.72 (dd, J = 6.0, 8.0 Hz, 1 H), 3.61 (d, J = 3.6 Hz, 1 H), 1.57 (s, 3 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.30 (d, J = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.22 (s, 3 H), 0.21 (s, 3 H), 0.15 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.6, 156.1, 136.7, 125.0, 114.0, 109.8, 105.5, 91.2, 87.9, 80.8, 76.7, 74.5, 69.7, 55.6, 55.4, 28.4, 26.5, 26.2, 23.6, 18.3, 16.2, 0.0, -3.5, -4.0; HRMS calcd for $C_{31}H_{52}NO_7{}^{28}Si_2$ $[M+H]^+$: 606.3277, found: 606.3268.



185 **187**

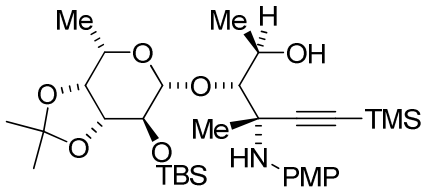
Ketone 187: Alkyne **185** (100 mg, 0.166 mmol) was added to a dry round bottomed flask in THF () under argon and was cooled to -78 °C. MeLi (1.6 M in Et_2O, 0.16 mL, 0.248 mmol) was then added dropwise over 5 minutes. The reaction was stirred for 1 h then quenched into a vigorously stirring mixture of $NaHCO_3$ saturated solution (25 mL) / EtOAc (25 mL) which was cooled in advance in an icebath. The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 25 mL). The organic fractions were combined, dried over Na_2SO_4, filtered, and solvent removed by vacuo. Purification by column chromatography (9:1, hexanes : ethyl acetate) provided ketone **187** (102.1 mg, 99%) as a clear residue.

$[\alpha]_D$ = +5.8 (*c* = 1.26, $CHCl_3$); IR (neat) 3341, 2955, 2165, 1714, 1510, 1249, 1072, 864, 840 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 8.8 Hz, 2 H), 4.33 (d, J = 8.4 Hz, 1 H), 4.10 (bs, 1 H), 3.99 (q, J = 5.6 Hz, 1 H), 3.97 (m, 1 H), 3.78 (s, 3 H), 3.76 (s, 1 H), 3.75 (m, 1 H), 3.65 (dd, J = 6.0, 8.0 Hz, 1 H), 2.38 (s, 3 H), 1.55 (s, 3 H), 1.35 (s, 6 H), 1.28 (d, J = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.26 (s, 3 H), 0.22 (s, 3 H), 0.15 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 156.2, 136.7, 126.5, 113.8, 109.6, 106.5, 104.0, 90.8, 89.9, 80.9, 76.8, 75.1, 69.7, 55.7, 55.6, 29.9, 28.4, 26.6, 23.7, 18.4, 16.2, 0.0, -3.4, -4.1; HRMS calcd for $C_{32}H_{54}NO_7{}^{28}Si_2$ $[M+H]^+$: 620.3433, found: 620.3434.



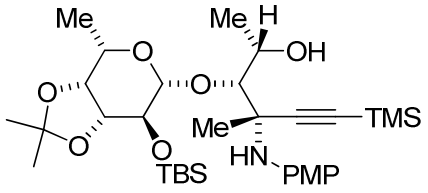
Secondary alcohol 188: $Zn(BH_4)_2$ was prepared by dropwise addition of zinc chloride (1.0 M in Et_2O) (2 mL, 2.0 mmol) to a strongly stirring, cold (icebath) suspension of sodium borohydride (151.4 mg, 4.0 mmol) in dry Et_2O (18 mL) under argon. The solution was stirred overnight, allowing the mixture to warm slowly to ambient temperature. The ether solution was filtered through a long plug of washed cotton, solvent removed by *vacuo*, and the resulting solid dried under high vacuum for >4 h The resulting zinc borohydride was obtained as a fine white powder that could be stored under argon for several days. (NOTE: $Zn(BH_4)_2$ should be a fine white powder. If there is any grey coloration to the zinc borohydride, the reducing reagent should not be used.) Ketone **187** (75.4 mg, 0.122 mmol) was then taken up in CH_2Cl_2 (12 mL) under argon, and cooled on an acetone bath (bath temperature -50 °C (±5 °C) maintained by a Neslab CC-100 chryostat). $Ti(OEt)_4$ (technical grade, 0.03 mL, 0.134 mmol) was added dropwise, and the solution was stirred for 0.5 h. $Zn(BH_4)_2$ (69.4 mg, 0.730 mmol) was added in one portion (NOTE: $Zn(BH_4)_2$ is not soluble in CH_2Cl_2), and reaction stirred for 24 h. Then added a second portion of Zn (46.4 mg, 0.488 mmol) and stirred an additional 18 h at -50 °C. Quenched reaction mixture into a cold (icebath) mixture of NH_4Cl saturated solution (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 50 mL), the organic fractions combined, dried over Na_2SO_4,

and solvent removed by *vacuo*. Secondary alcohols were separated and purified by column chromatography (9:1 → 85:15 → 7:3 → 1:1 → 3:7, hexanes : ethylether) to provide alcohol **188** (43.1 mg, 57%) as a residue and **189** (16.1 mg, 21%) as a crystalline white solid.



188

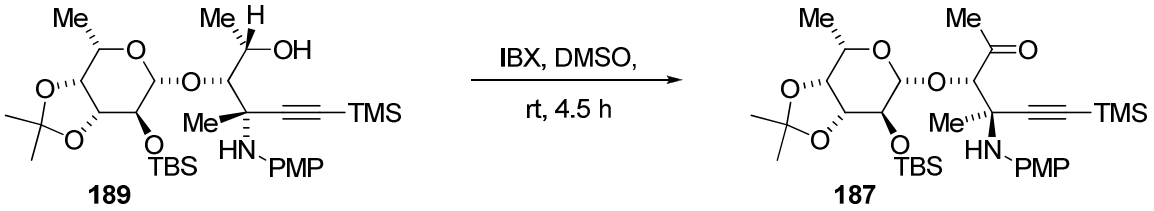
Alcohol 188: $[\alpha]_D$ = +57 (*c* = 0.105, $CHCl_3$); IR (neat) δ 3493, 3356, 2954, 2934, 2857, 2166, 1510, 1248, 1068, 1040, 840 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.04 (d, J = 9.2 Hz, 2 H), 6.78 (d, J = 9.2 Hz, 2 H), 4.49 (d, J = 7.6 Hz, 1 H), 4.15 (dq, J = 2.8, 6.8 Hz, 1 H), 4.01 (m, 2 H), 3.91 (dq, J = 1.2, 6.8 Hz, 1 H), 3.78 (s, 3 H), 3.75 (d, J = 2.8 Hz, 1 H), 3.62 (m, 1 H), 1.54, (s, 3 H), 1.44 (s, 3 H), 1.41 (d, J = 6.8 Hz, 3 H), 1.39 (d, J = 6.0 Hz, 3 H), 1.35 (s, 3 H), 0.89 (s, 3 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 137.4, 124.6, 113.8, 109.7, 107.6, 103.5, 91.1, 88.9, 80.7, 76.6, 74.7, 69.5, 67.8, 56.9, 55.7, 28.3, 26.5, 26.3, 24.2, 20.1, 18.4, 16.6, 0.0, -3.5, -4.2; HRMS calcd for $C_{32}H_{56}NO_7{}^{28}Si_2$ $[M+H]^+$: 622.3590, found: 622.3583.



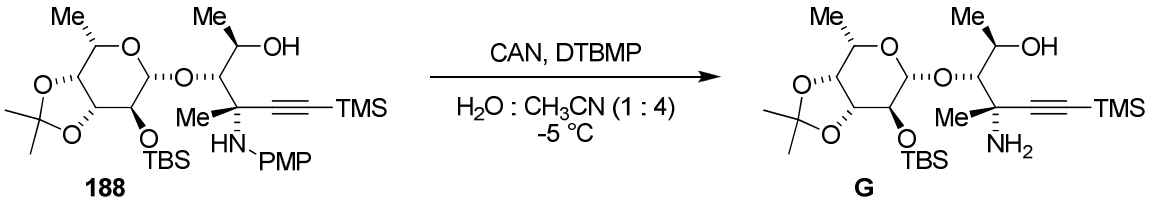
189

Alcohol 189: m.p.: 105 °C – 107 °C; $[\alpha]_D$ = +34 (*c* = 0.140, $CHCl_3$); IR (neat) 3513, 3340, 2934, 2857, 2166, 1511, 1249, 1040, 841 cm^{-1}; ^1H (400 MHz,

$CDCl_3$) δ 7.03 (d, J = 9.2 Hz, 2 H), 6.77 (d, J = 8.8 Hz, 2 H), 4.53 (d, J = 6.8 Hz, 1 H), 4.47 (dq, J = 3.2, 6.8 Hz, 1 H), 4.02 (m, 2 H), 3.89 (q, J = 6.8 Hz, 1 H), 3.78 (s, 3 H), 3.66 (m, 1 H), 3.54 (d, J = 2.8 Hz, 1 H), 1.54 (s, 3 H), 1.51 (s, 3 H), 1.39 (d, J = 6.8 Hz, 3 H), 1.35 (s, 3 H), 1.35 (d, J = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.17 (s, 6 H), 0.15 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 137.9, 123.4, 113.9, 109.7, 107.5, 103.4, 91.7, 85.8, 80.4, 76.5, 74.5, 69.1, 67.7, 58.6, 55.7, 28.0, 26.4, 26.2, 25.1, 21.7, 18.3, 16.7, -0.1, -3.7, -4.1; HRMS calcd for $C_{32}H_{56}NO_7{}^{28}Si_2$ $[M+H]^+$: 622.3590; found: 622.3589.



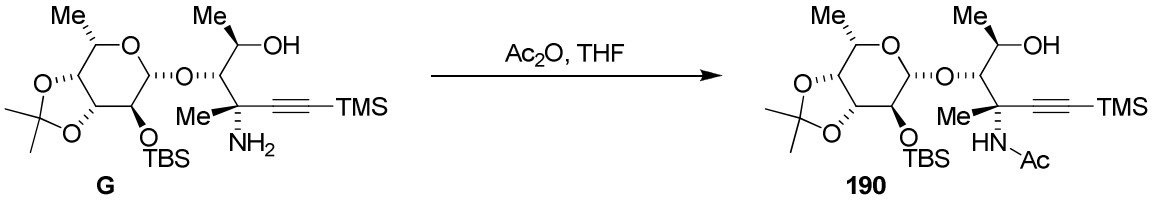
Oxidation of 189 to Ketone 187: In a dry 10 mL round bottomed flask was added **189** (74.2 mg, 0.119 mmol) in DMSO (4.0 mL), then added IBX (100.0 mg, 0.357 mmol) and the reaction mixture stirred at ambient temperature. After 4.5 h the reaction appeared complete by TLC. The reaction mixture was quenched into cold (ice bath) $NaHCO_3$ saturated solution (35 mL) and EtOAc (35 mL) under strong stirring. The layers were separated, and the aqueous phase extracted with EtOAc (2 × 35 mL). The organic fractions were combined, dried over Na_2SO_4, and removed solvent under reduced pressure. The crude mixture was then chromatographed (85:15, hexanes : EtOAc) to provide ketone **187** (62.8 mg, **85%**).



Amine G: Secondary alcohol **188** (38.0 mg, 0.061 mmol) was transfered with acetonitrile (2.4 mL) to a round bottomed flask containing 2,6-di-*tert*-butyl-4-methylpyridine (52.7 mg, 0.257 mmol) and cooled to -5 °C (ice/brine bath). Ammonium cerium nitrate (133.8 mg, 0.244 mmol) was taken up in H_2O (de-ionized, 0.6 mL) and added to the acetonitrile solution dropwise. (COLOR CHANGE: the reaction will turn darker with each additional drop of CAN solution, and will turn dark-brown – black over the course of the reaction). The solution was stirred for 3.5 h at -5 °C, then quenched into a cold (icebath) stirring mixture of $NaHCO_3$ saturated solution (35 mL) and ethyl acetate (25 mL). The phases were separated, and the aqueous layer extracted with additional ethyl acetate (2 $\times$ 25 mL), the organic fractions combined, dried over Na_2SO_4, and solvent removed by *vacuo*. Chromatrography (6:4 $\rightarrow$ 1:1, $\rightarrow$ 4:6, hexanes : ethyl acetate) provided primary amine **G** (18.4 mg, 58%) as a residue.

$[\alpha]_D$ = +8.8 (*c* = 0.635, $CHCl_3$); IR (neat) 3490, 3371, 2933, 2858, 2164, 1381, 1251, 1069, 842 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 4.36 (d, J = 8.0 Hz, 1 H), 3.99 (m, 2 H), 3.90 (m, 1 H), 3.98 (dq, J = 2.4, 6.4 Hz, 1 H), 3.58 (m, 1 H), 3.51 (d, J = 2.4 Hz, 1 H), 1.54 (s, 3 H), 1.41 (d, J = 6.8 Hz, 3 H), 1.40 (s, 3 H), 1.36 (d, J = 6.8 Hz, 3 H), 1.34 (s, 3 H), 0.92 (s, 9 H), 0.19 (s, 3 H), 0.18 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.4, 109.7, 104.0, 91.0, 88.3, 81.0, 76.8, 74.9, 69.6,

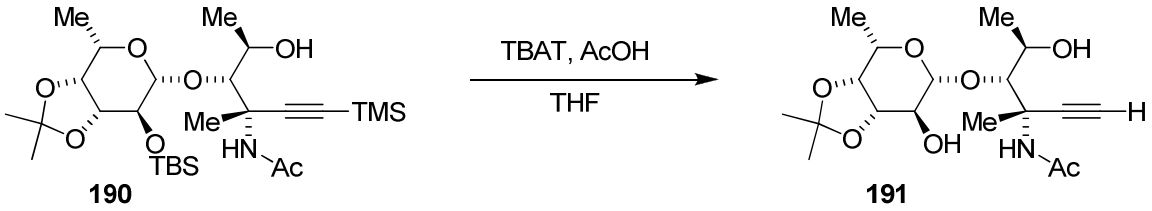
67.1, 51.4, 28.4, 27.9, 26.6, 26.3, 19.3, 18.3, 16.6, 0.0, -3.5, -4.0; HRMS calcd for $C_{25}H_{50}NO_6{}^{28}Si_2$ $[M+H]^+$: 516.3171, found: 516.3170.



G **190**

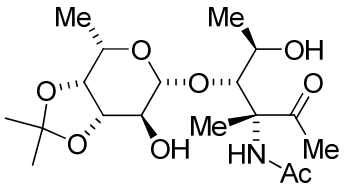
Acetamide 190: Primary amine **G** (18.4 mg, 0.036 mmol) was taken up in THF (3.6 mL) in a dry 5 mL round bottomed flask under argon, and acetic anhydride (0.004 mL, 0.037 mmol) was added. The reaction was stirred for 6 h at ambient temperature. The solvent was then removed by *vacuo*, and crude material chromatographed (6 : 4, hexanes : ethyl acetate) to provide acetamide **190** (16.4 mg, 82%) as a clear residue.

m.p. = 52 °C – 54 °C; $[\alpha]_D$ = +4.6 (*c* = 0.560, $CHCl_3$); IR (neat) 3450, 3300, 2933, 2858, 2174, 1667, 1371, 1250, 1136, 1068, 1040, 865, 842 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 5.74 (s, 1 H), 4.03 (d, J = 1.6 Hz, 1 H), 3.99 (d, J = 8.0 Hz, 1 H), 3.83 (m, 3 H), 3.76 (dq, J = 2.0, 6.8 Hz, 1 H), 3.72 (d, J = 10.4 Hz, 1 H), 3.43 (dd, J = 6.4, 7.6 Hz, 1 H), 1.79 (s, 3 H), 1.62 (s, 3 H), 1.38 (s, 3 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.20 (d, J = 6.4 Hz, 3 H), 1.19 (s, 3 H), 0.78 (s, 9 H), 0.03 (s, 6 H), 0.00 (s, 9 H); ^{13}C (100 MHz, $CDCl_3$) δ 169.5, 109.7, 105.7, 103.4, 90.2, 86.3, 80.7, 76.6, 74.6, 69.6, 67.2, 55.1, 28.3, 26.4, 26.3, 25.6, 24.7, 19.3, 18.5, 16.5, -0.1, -3.3, -4.4; HRMS calcd for $C_{27}H_{52}NO_7{}^{28}Si_2$ $[M+H]^+$: 558.3277, found: 558.3277.



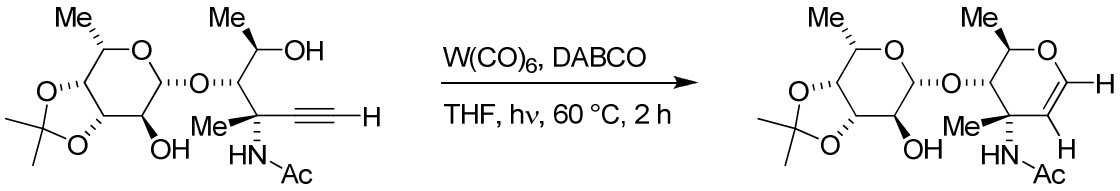
Alkyne alcohol 191: In a dry 5 mL round bottomed flask was added alcohol **190** (12.9 mg, 0.02 mmol) in THF (2.3 mL) at 0° C under argon. Acetic acid (0.01 mL, 0.19 mmol) was added, followed by TBAT (103.0 mg, 0.185 mmol), and the reaction mixture was allowed to warm to rt over 1 h. After 7 d, the reaction was complete by TLC. The reaction was then poured into cold (ice-bath) ammonium chloride saturated solution (10 mL) and ethyl acetate (10 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (2 × 10 mL), the organic fractions combined, dried over Na_2SO_4, and solvent removed by vacuo. Column chromatorgraphy (9:1 → 1:0, ethyl acetate : hexanes) provided alkynol **191** (7.2 mg, 84%) as a white residue.

$[\alpha]_D$ = -4.0 (*c* = 0.22, $CHCl_3$); IR (neat) 3415, 3302, 2986, 2936, 2876, 2115, 1665, 1538, 1447, 1379 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.28 (s, 1 H), 4.22 (d, J = 8.0 Hz, 1 H), 4.03 (m, 3 H), 3.95 (dq, J = 2.0, 6.4 Hz, 1 H), 3.65 (m, 2 H), 3.34 (bs, 1 H), 2.49 (s, 1 H), 1.97 (s, 3 H), 1.80 (s, 3 H), 1.56 (s, 3 H), 1.42 (d, J = 6.0 Hz, 3 H), 1.37 (s, 3 H), 1.35 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 110.3, 104.4, 89.0, 84.1, 79.3, 77.4, 76.3, 73.7, 69.8, 67.0, 54.5, 28.5, 26.5, 24.9, 24.6, 18.9, 16.7; HRMS calcd for $C_{18}H_{30}NO_7$ $[M+H]^+$: 372.2017, found 372.2012.



192

Ketone side product 192: m.p. = 52 °C – 53 °C, $[\alpha]_D$ = +26 (*c* = 0.20, $CHCl_3$); IR (neat) 3466, 2983, 2930, 2856, 1713, 1669, 1380, 1220, 1039 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 4.27 (d, J = 8.0 Hz, 1 H), 4.10 (dq, J = 6.4, 8.8 Hz, 1 H), 4.04 (dd, J = 5.6, 7.2 Hz, 1 H), 3.98 (dd, J = 1.6, 5.2 Hz, 1 H), 3.85 (d, J = 8.4 Hz, 1 H), 3.84 (dq, J = 2.4, 6.8 Hz, 1 H), 3.50 (dd, J = 5.2, 7.6 Hz, 1 H), 2.85 (bs, 1 H), 2.31 (s, 3 H), 1.95 (s, 3 H), 1.54 (s, 3 H), 1.41 (d, J = 6.4 Hz, 3 H), 1.40 (d, J = 6.8 Hz, 3 H), 1.36 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 157.0, 110.1, 103.0, 79.5, 76.4, 76.2, 74.2, 70.6, 69.5, 66.0, 28.4, 26.5, 25.6, 21.4, 21.2, 18.7, 16.8; HRMS calcd for $C_{18}H_{32}NO_8$ $[M+H]^+$: 390.2122, found: 390.2123.

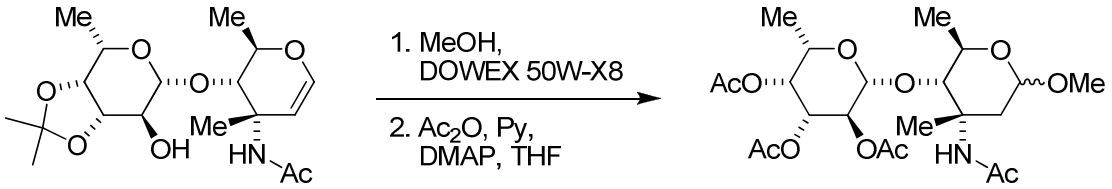


191 **193**

Saccharosamine glycal 193: Alkynol **191** (7.2 mg, 0.02 mmol) was added in THF (1.3 mL) in a dry 5-mL round bottomed flask containing 1,4-diazabicyclo[2.2.2]octane (4.3 mg, 0.04 mmol) and tungsten hexacarbonyl (1.8 mg, 5.0 μmol) under argon. A reflux condenser was fixed to the flask, and the reaction mixture was exposed to hν (350 nm, Rayonet Photoreactor) and allowing the reaction to warm to reflux. The reaction was stirred for 3 hours, then

filtered through a short plug of celite with ethyl acetate, and chromatographed (ethyl acetate) to provide glycal **193** (7.1 mg, 93%).

m.p. = 69 ℃ – 71 ℃; $[\alpha]_D$ = +67.5 (*c* = 0.405, $CHCl_3$); IR (neat) 3347, 2984, 2934, 2875, 1652, 1380, 1247, 1071 cm^{-1}; ^1H (, $CDCl_3$) δ 6.29 (d, J = 6.4 Hz, 1 H) 5.60 (s, 1 H), 4.95 (bs, 1 H), 4.80 (d, J = 6.0 Hz, 1 H), 4.31 (d, J = 8.0 Hz, 1 H), 4.07 (dd, J = 5.2, 6.8 Hz, 1 H), 3.99 (dd, J = 2.0, 5.2 Hz, 1 H), 3.90 (dq, J = 6.4, 9.6 Hz, 1 H) 3.82 (dq, J = 2.0, 6.8 Hz, 1 H), 3.51 (dd, J = 7.2, 8.0 Hz, 1 H), 3.41 (d, J = 10.4 Hz, 1 H), 1.98 (s, 3 H), 1.68 (s, 3 H), 1.54 (s, 3 H), 1.44 (d, J = 6.8 Hz, 3 H), 1.39 (d, J = 6.4 Hz, 3 H), 1.36 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 144.1, 110.0, 106.1, 105.7, 85.3, 79.7, 76.3, 73.7, 71.2, 69.3, 54.4, 28.4, 26.6, 25.4, 23.7, 18.4, 16.8; HRMS calcd for $C_{18}H_{30}NO_7$ $[M+H]^+$: 372.2017, found: 372.2016.



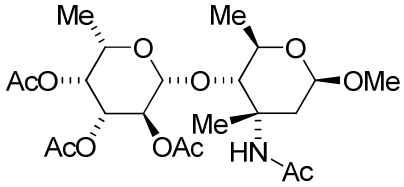
193 **194 + 137**

L-Fucose-D-saccharosamine disaccharides 194 and 137: In a dry vial was added glycal **193** (7.1 mg, 0.02 mmol) in methanol (1.9 mL) at rt under argon atmosphere. DOWEX 50W-X8 (14.2 mg) was then added in one portion and the reaction stirred for 16 h at ambient temperature. The crude reaction mixture was filtered through a short plug of celite with additional methanol (5 mL), and solvent removed by vacuo.

^1H (400 MHz, CD_3OD) δ 4.57 (dd, J = 0.8, 2.8 Hz, 1 H), 4.45 (dd, J = 1.2, 6.4 Hz, 1 H), 4.35 (m, 2 H), 4.00 (dq, J = 6.6, 9.6 Hz, 1 H), 3.78 (dq, J = 6.0, 9.6 Hz, 1 H),

3.63 (m, 2 H), 3.60 (m, 2 H), 3.49 (m, 2 H) 3.48 (m, 2 H), 3.41 (s, 3 H), 3.27 (s, 3 H), 3.26 (dd, J = 1.8, 13.8 Hz, 1 H), 3.22 (d, J = 9.6 Hz, 1 H), 3.16 (d, J = 9.6 Hz, 1 H), 3.07 (m, J = 14.4 Hz, 1 H), 1.95 (s, 3 H), 1.89 (s, 3 H), 1.64 (dd, J = 2.8, 14.4 Hz, 1 H), 1.44 (s, 3 H), 1.42 (2, 3 H), 1.38 (d, J = 6.0 Hz, 3 H); 1.35 (d, J = 6.6 Hz, 3 H), 1.27 (m, 1 H), 1.26 (d, J = 6.0 Hz, 3 H), 1.25 (d, J = 6.6 Hz, 3 H).

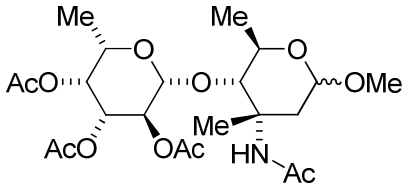
The crude reaction mixture was then taken up in THF (1.9 mL) in a dry 5 mL round bottomed flask, at rt under argon. Pyridine (5.0 μL, 0.06 mmol) was added, followed by Ac_2O (10 μL, 0.11 mmol) and DMAP (0.3 mg, 2.0 μmol). The reaction was then stirred for 12 h until reaction appeared complete by thin layer chromatography. Solvent was then removed by vacuo, and the crude reaction mixture chromatographed: 85:15 → 7:3, hexanes : ethyl acetate, yielding disaccharide **194** (2.9 mg, 31%) as a clear residue, along with an inseparable fraction of **194** and **137** as a 1:1 mixture (3.2 mg, 34%) .



194

Disaccharide 194: $[\alpha]_D$ = -7 (*c* = 0.14, CH_2Cl_2); IR (neat) 3404, 2926, 2854, 1749, 1223, 1070 cm^{-1}; ^1H (400 MHz, $(CD_3)_2SO$) δ 6.39 (s, 1 H), 5.14 (dd, J = 3.6, 10.0 Hz, 1 H), 5.10 (app d, J = 3.6 Hz, 1 H), 4.96 (dd, J = 8.4, 10.0 Hz, 1 H), 4.83 (d, J = 8.0 Hz, 1 H), 4.31 (app d, J = 9.2 Hz, 1 H), 4.04 (app q, J = 5.6 Hz, 1 H), 3.79 (dq, J = 6.0, 9.2 Hz, 1 H), 3.28 (s, 3 H), 3.13 (d, J = 9.6 Hz, 1 H), 2.94 (d, J = 13.2 Hz, 1 H), 2.13 (s, 3 H), 1.97 (s, 3 H), 1.93 (s, 3 H), 1.82 (s, 3 H), 1.39 (s, 3 H), 1.23 (d, J = 6.0 Hz, 3 H), 1.19 (dd, J = 10.0, 13.2 Hz, 1 H), 1.07 (d, J = 6.4

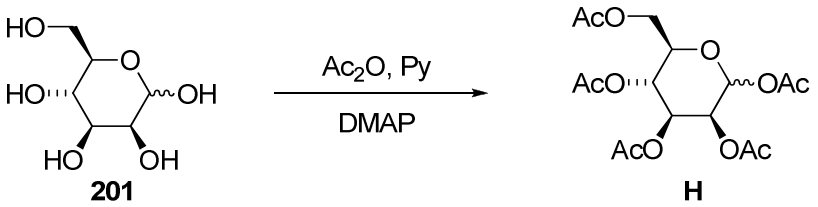
Hz, 3 H); ^{13}C NMR (600 MHz, $(CD_3)_2SO$) δ 170.8, 170.6, 170.4, 170.3, 102.7, 99.6, 85.5, 71.0, 70.1, 70.0, 69.4, 69.3, 56.8, 56.7, 38.6, 29.9, 24.7, 24.1, 21.2, 20.9, 18.8, 16.1; HRMS calcd for $C_{22}H_{36}NO_4$ $[M+H]^+$: 490.2283, found: 490.2281.



194 + 137

Disaccharide 194 and 137 mix: ^{1}H (400 MHz, $CDCl_3$) δ 5.72 (s, 1 H), 5.61 (s, 2 H), 5.24 (app d, J = 3.2 Hz, 3 H), 5.19 – 5.13 (m, 3 H), 5.07 – 5.03 (m, 3 H), 4.60 – 4.58 (m, 2 H), 4.55 (d, J = 7.6 Hz, 2 H), 4.41 (dd, J = 1.6, 10.0 Hz, 2 H), 3.89 – 3.76 (m, 3 H), 3.66 – 3.59 (m, 3 H), 3.45 (s, 6 H), 3.38 (dd, J = 1.6, 14.4 Hz, 2 H), 3.33 (app d, J = 15.2 Hz, 1 H), 3.27 (s, 3 H), 3.17 (d, J = 9.6 Hz, 1 H), 3.10 (d, J = 9.6 Hz, 2 H), 2.19 (s, 3 H), 2.18 (s, 6 H), 2.05 (s, 6 H), 2.04 (s, 3 H), 2.01 (s, 6 H), 2.00 (s, 3 H), 1.99 (s, 6 H), 1.93 (s, 3 H), 1.59 – 1.43 (m, 1 H), 1.46 (s, 3 H), 1.41 (s, 6 H), 1.39 – 1.32 (m, 2 H), 1.36 (d, J = 6.4 Hz, 6 H), 1.32 (d, J = 6.0 Hz, 3 H), 1.21 (d, J = 6.4 Hz, 3 H), 1.20 (d, J = 6.4 Hz, 6 H).

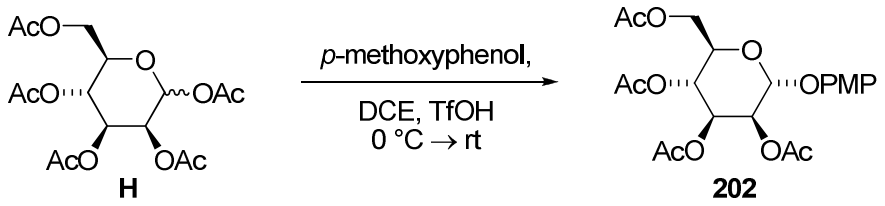
3.1.3. Experimental procedures of section 2.3



Peracyl-D-mannose H: In a dry 100 mL round bottomed flask was added D-mannose (10.0 g, 55.5 mmol) in acetic anhydride (60 mL) with pyridine (27 mL, 333 mmol) at rt under argon. DMAP (339 mg, 2.8 mmol) was added, and the reaction stirred overnight (12 h). (D-mannose is not soluble in acetic anhydride. The reaction becomes clear as the compound is acetylated.) The reaction was then poured into a slow-stirring, cold (ice bath) mixture of $NaHCO_3$ saturated solution (500 mL) and CH_2Cl_2 (250 mL) over 3 h. The layers were then separated, the aqueous phase extracted with CH_2Cl_2 (2 × 200 mL), and the organic fractions combined. After drying over Na_2SO_4, solvent was removed by *vacuo*, and the crude reaction mixture chromatographed (6:4 → 1:1, hexanes : ethyl acetate) to provide peracetylated mannose **H** (21.65 g, >99%) as a 2:1 mixture of α:β anomers.

IR (neat) 2991, 2960, 1751, 1371, 1221, 1053 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.07 (d, J = 2.0, 2 H), 5.84 (d, J = 1.2 Hz, 1 H), 5.47 (dd, J = 1.2, 2.8 Hz, 1 H), 5.34 – 5.30 (m, 4 H), 5.24 (m, 3 H), 5.12, (dd, J = 3.2, 9.6 Hz, 1 H), 4.79 (ddd, J = 2.4, 5.6, 10.4 Hz, 1 H), 4.29 (dd, J = 5.2, 12.8 Hz, 1 H), 4.27 (dd, J = 4.8, 12.4 Hz, 2 H), 4.12 (dd, J = 2.4, 12.8 Hz, 1 H), 4.08 (dd, J = 2.0, 12.4 Hz, 2 H), 4.03 (m, 2 H), 2.20 (s, 3 H), 2.16 (s, 6 H), 2.15 (s, 6 H), 2.09 (s, 3 H), 2.08 (s, 9 H), 2.04 (s, 9 H), 1.99 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.2, 170.0, 169.8,

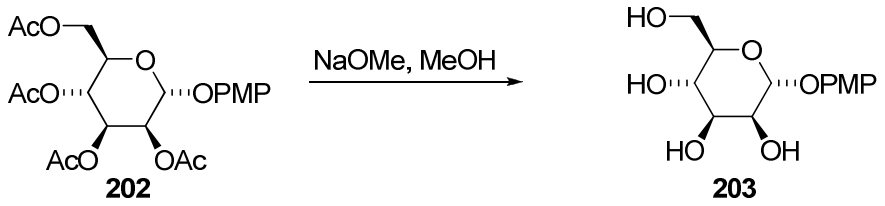
168.6, 168.3, 90.8, 90.6, 70.8, 70.8, 73.5, 68.9, 68.5, 68.3, 65.7, 65.5, 62.3, 21.1, 21.0, 20.9, 20.9, 20.8; HRMS calcd for $C_{14}H_{19}O_9$ $[M\text{-}OAc]^+$: 331.1024, found: 331.1022.



C1-(*p*-methoxyphenyl)-peracyl-D-mannose 202: In a dry 250 mL round bottomed flask was added peracetylated mannose **H** in DCE (171 mL) and the reaction was cooled to 0 ℃ (ice bath) under argon. *p*-Methoxyphenol (13.7 g, 110 mmol) was then added, followed by triflic acid (0.74 mL, 8.33 mmol). The reaction was allowed to warm to rt over 3h and stirred overnight (8 h). The reaction was poured into a strongly stirring mixture of $NaHCO_3$ saturated solution (150 mL) and ethyl acetate (150 mL). The layers were separated, the aqueous phase then extracted with ethyl acetate (2 × 150 mL), the organic fractions combined, dried over Na_2SO_4, and solvent removed by *vacuo*. The crude reaction mixture was then chromatographed (85:15 → 7:3, hexanes : ethyl acetate) to provide the mannose **202** (17.08 g, 68%).

m.p. = 101 ℃ – 103 ℃; $[\alpha]_D$= +71.2 (*c* = 0.535, $CHCl_3$); IR (neat) 2956, 1749, 1509, 1218, 1038 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.00 (d, J = 9.2 Hz, 2 H), 6.80 (d, J = 9.2 Hz, 2 H), 5.53 (dd, J = 3.6, 10.4 Hz, 1 H), 5.41 (dd, J = 2.0, 3.6 Hz, 1 H), 5.39 (d, J = 2.0 Hz, 1 H), 5.34 (dd, J = 10.4, 10.0 Hz, 1 H), 4.26 (dd, J = 5.2, 12.0 Hz, 1 H), 4.11 (m, 1 H), 4.06 (dd, J = 2.4, 12.4 Hz, 1 H), 3.75 (s, 3 H), 2.17 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8,

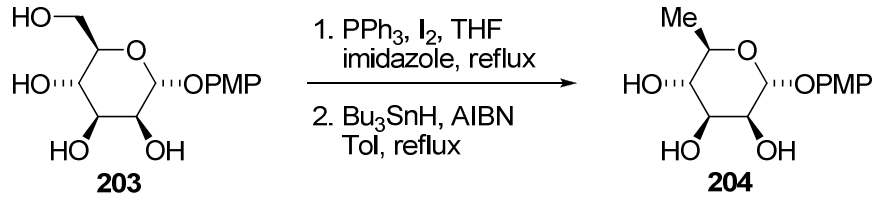
170.3, 170.2, 170.0, 155.6, 149.8, 118.0, 114.8, 96.8, 69.7, 69.2, 69.1, 66.2, 62.4, 55.8, 21.1, 20.9; HRMS calcd for $C_{21}H_{27}O_{11}$ $[M+H]^+$: 455.1548, found: 455.1555.



202 **203**

C1-(*p*-methoxyphenyl)-D-mannose 203: In a 250 mL round bottomed flask was transferred mannoside **202** (9.962 g, 0.022 mol) in methanol (100 mL) at rt under argon. NaOMe (0.5 M in methanol, 22 mL, 11 mmol), was added, and the reaction stirred overnight (11 h). Solvent was then removed by *vacuo*, and the crude reaction mixture chromatographed (95:5 → 9:1, chloroform : methanol) to provide α-C1 (*p*-methoxy phenoxy)mannose **203** (5.556 g, 88%).

^{1}H (400 MHz, CD_3OD) δ 7.04 (d, J = 8.8 Hz, 2 H), 6.83 (d, J = 9.6 Hz, 2 H), 5.33 (d, J = 2.0 Hz, 1 H), 3.98 (dd, J = 2.0, 3.6 Hz, 1 H), 3.88 (dd, J = 3.6, 8.8 Hz, 1 H), 3.78 (dd, J = 2.4, 12.0 Hz, 1 H), 3.74 (s, 3 H), 3.71 (m, 2 H), 3.64 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.4, 150.4, 118.0 114.3, 99.9, 74.0, 71.2, 70.9, 67.2, 61.5, 54.8.

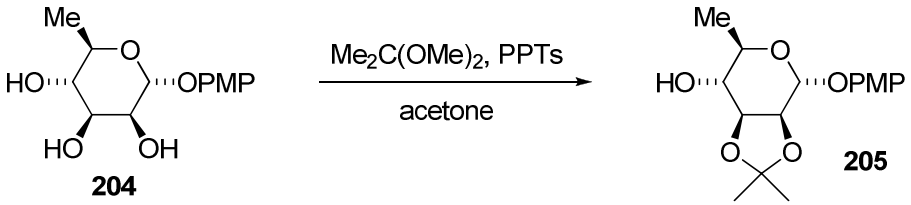


203 **204**

Rhamnose triol 204: Alcohol **203** (2.474 g, 8.642 mmol) was charged in THF (88.8 mL) in a dry 250 mL round bottomed flask, at rt under argon. Triphenyl phosphine (3.456 g, 13.18 mmol) was added in one portion, followed by

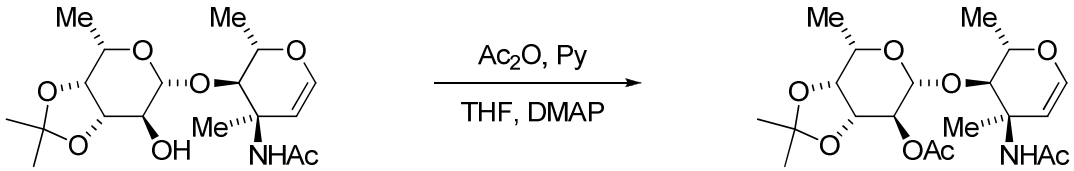
imidazole (1.196 g, 17.57 mmol). The reaction mixture was heated to reflux and stirred for 30 min, then cooled back to rt. Iodine (3.345 g, 13.18 mmol) was then added, the mixture heated again to reflux and stirred for 2 h. The reaction was then cooled to rt, and poured into a strongly stirring, cold (icebath) solution of $NaHCO_3$ saturated solution (150 mL) and ethyl acetate (150 mL). The layers were separated, and the aqueous phase extracted with ethyl acetate (2 × 100 mL). The organic fractions were then combined, dried over Na_2SO_4, and solvent removed by *vacuo*. Crude Iodide was then carried on without further purification. The crude iodide was then added to a dry 250 mL round bottomed flask with Bu_3SnH (3.44 mL, 13.0 mmol), azobisisobutyrlnitrile (141.9 mg, 0.86 mmol), and toluene (173 mL). The reaction was heated to reflux with stirring for 2 h, then allowed to cool to room temperature. The solvents were removed by *vacuo*, and the crude mixture chromatographed (9:1, hexanes : ethyl acetate) providing triol **204** as a white solid (2.11 g, 90%).

m.p. = 101 ℃ – 102 ℃; $[\alpha]_D$= +117.7 (*c* = 0.370, MeOH); IR (neat) 3345, 2934, 2835, 1509, 1217, 1121, 1063, 1033, 983, 827 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.99 (d, J = 9.2 Hz, 2 H), 6.83 (d, J = 9.2 Hz, 2 H), 5.41 (d, J = 1.6 Hz, 1 H), 4.16 (dd as app. bs, 1 H) 3.99 (dd, J = 1.2, 4.4 Hz, 1 H), 3.82 (dq, J = 6.4, 9.6 Hz, 1 H), 3.56 (app. t, J = 9.2 Hz, 1 H), 2.96 (bs, 1 H), 2.74 (bs, 1 H), 2.59 (bs, 1 H), 3.78 (s, 3 H), 1.30 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.3, 117.8, 114.8, 98.6, 73.7, 71.8, 71.1, 68.6, 55.8, 17.7; HRMS calcd for $C_{13}H_{19}O_6$ $[M+H]^+$: 271.1176, found: 271.1180.



Acetonide 205: Triol **204** (150 mg, 0.56 mmol) was taken up in acetone (5.6 mL, dried over drierite for 1 h), and 2,2-dimethoxypropane (0.68 mL, 5.55 mmol) was added, followed by pyridinium *p*-toluenesulfonate (14.1 mg, 0.06 mmol), and the reaction was stirred at room temperature overnight (10 h). The reaction was then poured into a stirring mixture of $NaHCO_3$ saturated solution (15 mL) and ethyl acetate (15 mL). The phases were separated, and the aqueous layer extracted with ethyl acetate (2 × 15 mL). The organic fraction were combined, dried over Na_2SO_4, solvent removed by *vacuo*, and the crude mixture chromatographed (85:15 hexanes : ethyl acetate) to provide acetonide **205** as a sticky white solid (147 mg, 85%).

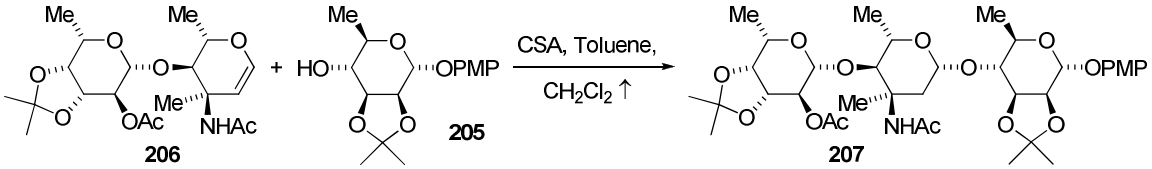
m.p. = 82 °C – 84 °C; $[\alpha]_D$= +70.9 (*c* = 0.495, $CHCl_3$); IR (neat) 3461, 2986, 2936, 2835, 1509, 1217, 1139, 1038, 994 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.00 (d, J = 9.2 Hz, 2 H), 6.84 (d, J = 9.2 Hz, 2 H), 5.61 (s, 1 H), 4.36 (d, J = 5.2 Hz, 1 H), 4.24 (dd, J = 6.0, 7.6 Hz, 1 H), 3.82 (dq, J = 6.4, 10.0 Hz, 1 H), 3.78 (s, 3 H), 3.46 (ddd, J = 4.4, 7.6, 10.0 Hz, 1 H), 2.74 (d, J = 4.4 Hz, 1 H); 1.57 (s, 3 H), 1.41 (s, 3 H), 1.25 (d, J = 6.4 Hz, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 155.1, 150.3, 117.9, 114.8, 109.9, 96.4, 78.7, 76.0, 74.8, 66.6, 55.8, 28.2, 26.5, 17.5; HRMS calcd for $C_{16}H_{23}O_6$ $[M+H]^+$: 311.1489, found: 311.1485.



182 **206**

Glycal donor 206: Glycal **182** (49.0 mg, 0.13 mmol) was taken up in THF (4.4 mL) at room temperature in a 10 mL round bottomed flask, under argon. Acetic anhydride (0.04 mL, 0.40 mmol) was added in one portion, followed by pyridine (0.02 mL, 0.26 mmol), then 4-*N*,*N*-dimethylaminopyridine (8.1 mg, 0.07 mmol). The reaction was stirred at ambient temperature for 8 h, then quenched into $NaHCO_3$ saturated solution (5 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous phase extracted with ethyl acetate (2 × 10 mL), the organic layers combined, dried over Na_2SO_4, solvent removed by vacuo, and the crude reaction chromatographed (1:1, hexanes : ethyl acetate) to provide peracethylated glycal **206** (49.3 mg, 90%) as a residue.

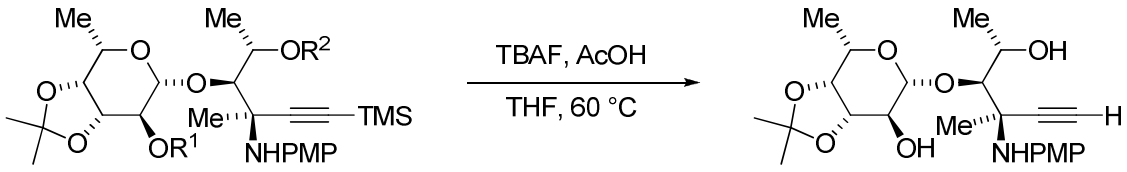
$[\alpha]_D$= -128 (*c* = 0.295, $CHCl_3$); IR (neat) 3398, 2985, 2937, 2879, 1747, 1674, 1510, 1375, 1227, 1076 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.18 (d, J = 6.0 Hz, 1 H), 6.09 (s, 1 H), 5.45 (d, J = 6.0 Hz, 1 H), 4.97 (dd, J = 8.0, 7.6 Hz, 1 H), 4.40 (d, J = 8.0 Hz, 1 H), 4.16 (dd, J = 5.6, 7.6 Hz, 1 H), 4.04 (dd, J = 2.0 4.8 Hz, 1 H), 3.87 (m, 2 H), 3.31 (d, J = 9.6 Hz, 1 H), 2.11 (s, 3 H), 1.91 (s, 3 H), 1.57 (s, 3 H), 1.45 (s, 3 H), 1.39 (d, J = 6.8 Hz, 3 H), 1.35 (s, 3 H), 1.30 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.1, 141.7, 110.5, 106.0, 100.5, 82.8, 76.8, 76.4, 73.5, 70.4, 69.4, 52.4, 28.0, 26.4, 24.7, 24.6, 21.3, 17.5, 16.5; HRMS calcd for $C_{20}H_{32}NO_8$ $[M+H]^+$: 414.2122, found: 414.2122.



Fucose-saccharosamine-rhamnose trisaccharide 207: Glycal **206** (6.5 mg, 16 μmol) was charged with toluene into a dry vial along with glycosyl acceptor **205** (24.4 mg, 0.08 mmol), solvent removed, and the mixture azeotroped twice with toluene. Toluene (5 drops) was added, followed by CH_2Cl_2 (0.32 mL), then camphorsulfonic acid (0.5 mg). The reaction was then stirred at ambient temperature, and the CH_2Cl_2 was driven off under a gentle flow of argon over 3 h. After 16 h, the reaction appeared complete. The reaction was quenched into $NaHCO_3$ saturated solution (5 mL) using ethyl acetate (5 mL). The layers were separated and the aqueous phase extracted (2 × 10 mL), the organic layers combined, dried over Na_2SO_4, solvent removed by vacuo, and the crude reaction mixture chromatographed (6:4 → 1:1, hexanes : ethyl acetate) to provide trisaccharide **207** (6.0 mg, 53%) as a residue.

$[\alpha]_D$= +34 (*c* = 0.285, CH_2Cl_2); IR (neat) 3402, 2985, 2933, 1747, 1680, 1508, 1444, 1373, 1221, 1136, 1072, 1039, 993 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.98 (d, J = 8.8 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 5.63 (s, 1H), 5.57 (d as app. s, 1 H), 4.98 (dd, J = 1.6, 9.6 Hz, 1 H), 4.94 (dd, J = 8.4, 7.6 Hz, 1 H), 4.35 (d, J = 8.0 Hz, 1 H), 4.30 (m, 2 H), 4.15 (dd, J = 5.2, 8.0 Hz, 1 H), 4.04 (dd, J = 2.0, 4.8 Hz, 1 H), 3.84 (dq, 2.0, 6.8 Hz, 1 H), 3.78 (s, 3 H), 3.77 (m, 1 H), 3.64 (dd, J = 6.8, 10.4 Hz, 1 H), 3.52 (dq, J = 9.2 Hz, 1 H), 3.49 (dd, J = 1.6, 14.0 Hz, 1 H), 3.07 (d, J = 9.2 Hz, 1 H), 2.13 (s, 3 H), 1.98 (s, 3 H), 1.59 (s, 3 H), 1.54 (s, 3 H), 1.44 (s, 3 H),

1.39 (d, J = 6.4 Hz, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.32 (dd, J = 14.8, 10.4 Hz, 1 H), 1.27 (d, J = 6.0 Hz, 3 H), 1.20 (d, J = 6.0 Hz, 3 H); HRMS calcd for $C_{36}H_{54}NO_{14}$ $[M+H]^+$: 724.3539, found: 724.3559.



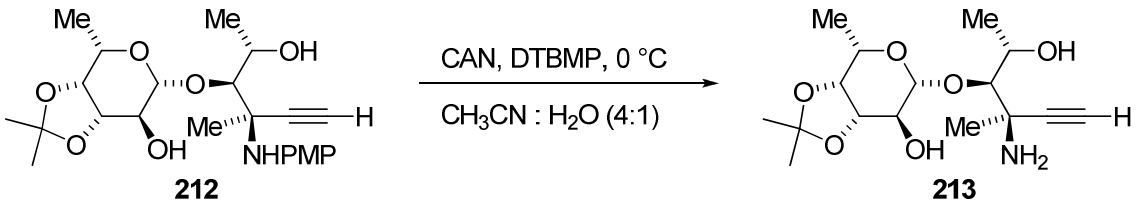
211 **212**

$R^1 \neq R^2$ R^1, R^2 = H or TBS

Diol 212: In a dry 25 mL round bottomed flask, fitted with a condensing column, was added alcohol **211** (2.649 g, 4.259 mmol, as a mixture of TBS-migrated isomers) in THF (21 mL). Acetic acid (2.05 mL, 34.1 mmol) was then added, followed by TBAF (1.0 M in THF, 20.0 mL, 20.0 mmol) and the reaction warmed to 60 °C with stirring. After 28 h, the reaction appeared complete by TLC, and was allowed to cool to rt, then quenched into a strongly stirring mixture of $NaHCO_3$ saturated solution (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL), the organic layers combined, dried over Na_2SO_4, solvent removed by *vacuo*, and the crude reaction mixture chromatographed (85:15 → 9:1 → 1:0, ethyl acetate : hexanes) to provide diol **212** (1.315 g, 71%).

$[\alpha]_D$: -109 (*c* = 0.280, CH_2Cl_2); ^1H (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.8 Hz, 2 H), 6.81 (2, J = 9.2 Hz, 2 H), 4.48 (d, J = 8.4 Hz, 1 H), 4.21 (dq, J = 2.0, 6.4 Hz, 1 H), 4.09 (dd, J = 5.6, 7.2 Hz, 1 H), 4.02 (dd, J = 2.0, 5.2 Hz, 1 H), 3.95 (dq, J = 2.0, 6.4 Hz, 1 H), 3.84 (d, J = 2.4 Hz, 1 H), 3.78 (s, 3 H), 3.76 (app t, J = 8.4 Hz, 1 H), 2.41 (s, 1 H), 1.58 (s, 3 H), 1.48 (s, 3 H), 1.47 (d, J = 5.6 Hz, 3 H), 1.43 (d, J = 6.0 Hz, 3 H), 1.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 138.1, 123.7,

114.1, 110.3, 105.2, 91.9, 84.6, 80.1, 76.5, 75.3, 74.2, 69.8, 55.7, 55.5, 28.5, 26.4, 24.6, 18.6, 16.8; HRMS calcd for $C_{33}H_{34}NO_7$ $[M+H]^+$: 436.2330, found: 436.2321.

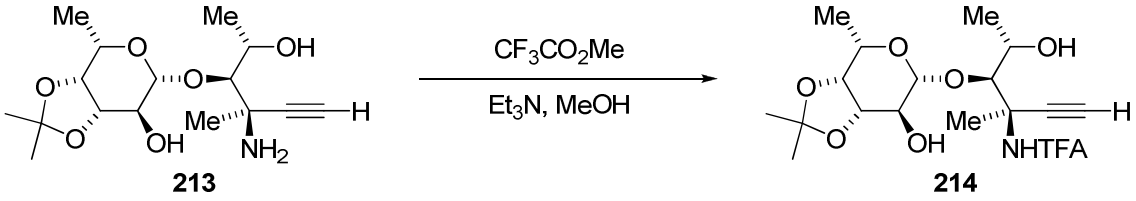


212 **213**

Amino diol 213: Diol **212** (1.102 g, 2.530 mmol) was taken up in CH_3CN (6.7 mL) with DTBMP (2.286 g, 11.13 mmol) at -5 °C (ice/brine bath), under open atmosphere. CAN (5.549 g, 10.12 mmol) was taken up in deionized H_2O (1.7 mL), and then added dropwise to the reaction mixture. After 5 h, the reaction appeared complete and turns a deep reddish-black. The reaction was then quenched into a cold (icebath) mixture of $NaHCO_3$ satured solution (75 mL) and ethyl acetate (75 mL). The layers were separated and the aqueous phase extracted with with ethyl acetate (10 × 50 mL), the organic fractions combined, dried over Na_2SO_4, solvent removed by *vacuo*, and the crude mixture chromatographed (98:2 → 95:5 → 9:1, chloroform : methanol) to provide aminodiol **213** (594.3 mg, 71%).

$[\alpha]_D$ = -49.5 (*c* = 0.19, CH_2Cl_2); IR (neat) 3350, 3290, 2987, 2877, 2117, 1381, 1070, 1034 cm^{-1}; ^1H (400 MHz, CD_3OD) δ 4.42 (d, J = 8.8, 1 H), 4.08 – 4.01 (m, 3 H), 3.95 (dq, J = 2.0, 6.8 Hz, 1 H), 3.56 (d, J = 2.8 Hz, 1 H), 3.51 (dd, J = 6.8, 8.0 Hz, 1 H), 2.78 (s, 1 H), 1.51 (s, 3 H), 1.40 (s, 3 H), 1.38 (d, J = 6.8 3 H), 1.35 (d, J = 6.8 Hz, 3 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 110.8, 105.9, 91.7,

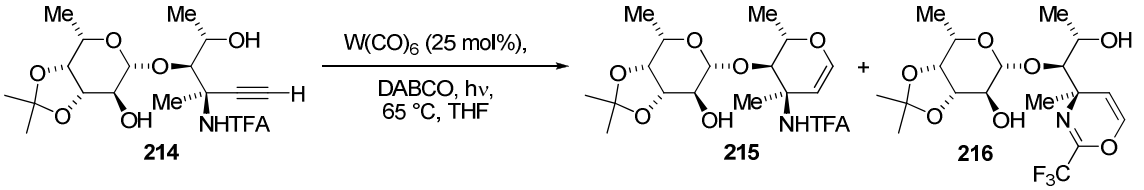
87.9, 81.3, 77.9, 75.2, 74.2, 70.5, 69.5, 51.8, 28.7, 27.4, 26.7, 18.8, 17.0; HMRS calcd for $C_{16}H_{28}NO_6$ $[M+H]^+$: 330.1911, found: 330.1903.



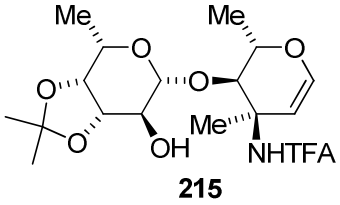
213 **214**

Trifluoroacetamide 214: In a dry 10 mL round bottomed flask was added amine **213** (54.1 mg, 0.164 mmol) in methanol (3.3 mL). Et_3N (0.23 mL, 1.6 mmol) was then added, followed by CF_3CO_2Me (0.33 mL, 3.3 mmol) and the reaction stirred at ambient temperature. After 2 hours the reaction appears complete by TLC. Solvent was removed by *vacuo* and the crude reaction mixture chromatographed (1:1 → 6:4 → 7:3, hexanes : EtOAc) to provide trifluoroacetamide **214** (60.2 mg, 86%).

m.p. = 189 °C – 191 °C; $[\alpha]_D$ = -104 (*c* = 0.038, CH_2Cl_2); IR (neat) 3498, 3425, 3261, 2987, 2943, 1720, 1566, 1221, 1153, 1066 cm^{-1}; ^1H (400 MHz, CD_3OD) δ 4.47 (d, J = 8.4 Hz, 1 H), 4.22 (dq, J = 5.2, 6.4 Hz, 1 H), 4.07 (dd, J = 2.0, 5.6 Hz, 1 H), 4.03 – 3.98 (m, 2 H), 3.73 (d, J = 4.8 Hz, 1 H), 3.48 (app. t, J = 8.4 Hz, 1 H), 2.86 (s, 1 H), 1.78 (s, 3 H), 1.49 (s, 3 H), 1.42 (d, J = 6.4 Hz, 3 H), 1.36 (d, J = 3.6 Hz, 3 H), 1.34 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 157.6, 157.4, 157.1, 156.9, 120.1, 118.2, 116.2, 114.3, 110.9, 104.4, 86.6, 82.6, 81.1, 77.9, 75.1, 74.8, 71.0, 69.3, 55.6, 28.6, 26.7, 24.5, 20.0, 16.7; HRMS calcd for $C_{18}H_{27}F_3NO_7$ $[M+H]^+$: 426.1734, found: 426.1734.



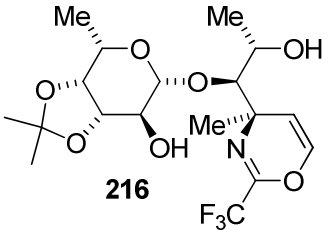
Glycal 215 and Oxazine 216: In a dry 5 mL round bottomed flask was added alkyne alcohol **214** (18.9 mg, 0.044 mmol) in THF (1.5 mL) with DABCO (10.0 mg, 0.089 mmol) and $W(CO)_6$ (3.9 mg, 0.011 mmol) under argon. The flask was fitted with a reflux condenser and the reaction exposed to hν (350 nm) at 65 °C for 6 h. The crude reaction mixture was then filtered through celite with EtOAc (15 mL) and solvent removed under reduced pressure. Chromatography (7:3 → 6 : 4 → 1 : 1, hexanes : EtOAc) provided glycal **215** (12.0 mg, 63%) and oxazine **216** (1.9 mg, 10 %). When the reaction was run in toluene at 45 °C oxazine **216** was preferred (56%) over glycal **215** (33%) on a 40 mg scale.



215

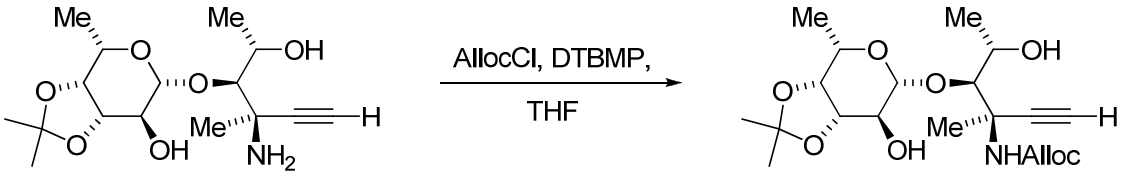
Glycal 215: $[\alpha]_D$ = -100 (*c* = 0.23, CH_2Cl_2); IR (neat) 3471, 3396, 2987, 2937, 2879, 1722, 1221, 1174, 1072 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.93 (bs, 1 H), 6.30 (d, J = 6.4 Hz, 1 H), 5.38 (d, J = 6.4 Hz, 1 H), 4.32 (d, J = 8.4 Hz, 1 H), 4.04 (m, 2 H), 3.90 (m, 2 H), 3.58 (app t, J = 7.2 Hz, 1 H), 3.45 (d, J = 9.6 Hz, 1 H), 2.51 (bs, 1 H), 1.57 (s, 3 H), 1.55 (s, 3 H), 1.45 (d, J = 6.4 Hz, 3 H), 1.39 (d, J = 6.8 Hz, 3 H), 1.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (q, J = 23.9, coupled to fluorine), 143.5, 115.9 (q, J =191.5 Hz, coupled to fluorine), 110.3, 103.8, 103.0,

83.2, 79.4, 76.3, 74.0, 70.9, 69.7, 53.5, 28.4, 26.4, 24.7, 17.7, 16.5; HRMS calcd for $C_{18}H_{27}F_3NO_7$ $[M+H]^+$: 426.1734, found 426.1725.



216

Oxazine 216: IR(neat) 3390, 2987, 2939, 2877, 1722, 1383, 1221, 1157, 1099, 1072, 1034 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.45 (d, J = 6.4 Hz, 1 H), 5.43 (d, J = 6.4 Hz, 1 H), 4.31 (d, J = 8.0 Hz, 1 H), 4.14 (dq, J = 5.6, 6.0 Hz, 1 H), 4.04 (dd, J = 5.2, 7.2 Hz), 3.99 (dd, 1.2, 5.2 Hz, 1 H), 3.83 (dq, J = 1.6, 6.4 Hz, 1 H), 3.61 (d, J = 5.2 Hz, 1 H), 3.56 (dd, J = 7.6, 8.0 Hz, 1 H), 3.21 (bs, 1 H), 1.54 (s, 3 H), 1.38 (d, J = 6.0 Hz, 3 H), 1.36 (app s, 6 H), 1.31 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (q, J = 39.4 Hz, coupled to fluorine), 137.1, 117.7 (q, J = 275.3 Hz, coupled to fluorine), 110.1, 109.8, 103.5, 87.8, 79.5, 76.5, 74.4, 69.6, 68.0, 56.6, 28.4, 26.4, 26.1, 19.6, 16.6.

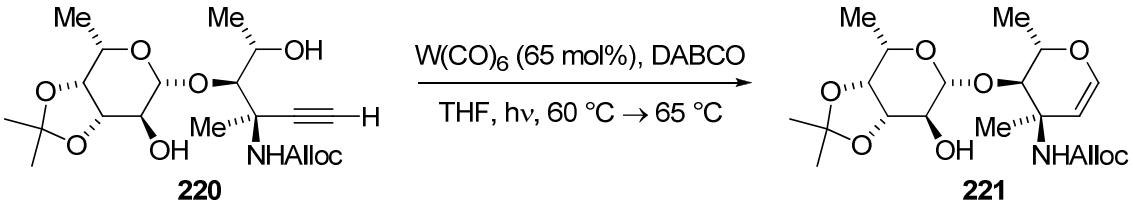


213 **220**

Carbamate 220: In a dry 25 mL round bottomed flask was added amine **213** (534.5 mg, 1.623 mmol) in THF at ambient temperature under argon. AllocCl (0.19 mL, 1.79 mmol) was added dropwise over 1 min. After 0.5 h, the reaction appeared complete by TLC, solvent was removed by *vacuo*, and the crude

reaction mixture chromatographed (8:2, hexanes : EtOAc) to provide carbamate **220** (542.7 mg, 81%).

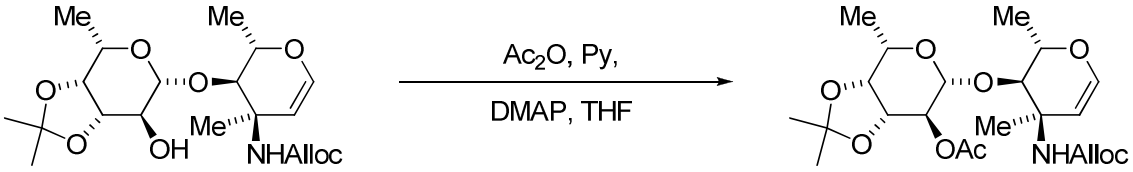
$[\alpha]_D$ = -76 (*c* = 0.170, CH_2Cl_2); IR (neat) 3396, 3307, 2987, 2939, 2879, 1724, 1531, 1381, 1250, 1068 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.42 (s, 1 H), 5.90 (ddd, J = 5.6, 10.4, 17.2 Hz, 1 H), 5.29 (dd, J = 1.6, 17.2 Hz, 1 H), 5.17 (dd, J = 1.2, 10.8 Hz, 1 H), 4.53 (m, 2 H), 4.37 (d, J = 8.4 Hz, 1 H), 4.12 (dq, J = 2.8, 6.4 Hz, 1 H), 4.04 (dd, J = 5.2, 6.8 Hz, 1 H), 3.99 (dd, J = 2.0, 5.2 Hz, 1 H), 3.91 (dq, J = 2.0, 6.4 Hz, 1 H), 3.67 (m, 2 H), 3.28 (bs, 2 H), 2.40 (s, 1 H), 1.69 (s, 3 H), 1.54 (s, 3 H), 1.42 (d, J = 6.8 Hz, 3 H), 1.39 (d, J = 6.8 Hz, 3 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 133.1, 117.9, 110.4, 105.0, 90.4, 83.4, 79.9, 76.4, 74.2, 73.2, 70.0, 68.1, 65.5, 52.2, 28.4, 26.5, 24.4, 18.3, 16.6; HRMS calcd for $[M+H]^+$: 414.2122, found: 414.2126.



220 **221**

Glycal 221: In a dry round bottomed flask was added alkyne alcohol **220** (515.6 mg, 1.247 mmol) in THF with DABCO (279.8 mg, 2.494 mmol) and $W(CO)_6$ (153.4 mg, 0.436 mmol). The reaction vessel was fitted with a condensing coil and exposed to 350 nm radiation at 60 °C – 65 °C for 5 h. An additional portion of $W(CO)_6$ (131.6 mg, 0.374 mmol) was added and the reaction stirred an additional 3.5 h. The crude reaction mixture was filtered through celite, and chromatographed (8:2, hexanes :EtOAc) to provide glycal **221** (448.5 mg, 87%).

$[\alpha]_D$ = -131.8 (*c* = 0.340, CH_2Cl_2); IR (neat) 3419, 2983, 2935, 2877, 1722, 1649, 1498, 1247, 1070 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.23 (d, J = 6.4 Hz, 1 H), 5.91 (ddd, J = 5.56, 10.8, 16.0 Hz, 1 H), 5.47 (bs, 1 H), 5.30 (d, J = 6.4 Hz, 1 H), 5.28 (dd, J = 1.2, 17.2 Hz, 1 H), 5.19 (dd, J = 1.2, 10.4 Hz, 1 H), 4.50 (d, J = 4.4, 2 H), 4.27 (d, J = 8.0 Hz, 1 H), 4.02 (m, 3 H), 3.83 (dq, J = 1.6, 6.4 Hz, 1 H), 3.55 (app t, J = 8.4 Hz, 1 H), 3.39 (d, J = 9.6 Hz, 1 H), 2.93 (bs, 1 H), 1.54 (s, 3 H), 1.45 (s, 3 H), 1.39 (d, J = 6.4 Hz, 3 H), 1.36 (d, J = 6.8 Hz, 3 H), 1.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 142.3, 133.2, 117.9, 110.1, 105.6, 102.6, 83.1, 79.3, 76.4, 73.8, 70.7, 69.4, 65.3, 51.7, 28.4, 26.4, 25.2, 17.7, 16.5; HRMS calcd for $C_{20}H_{32}NO_8$ $[M+H]^+$: 414.2122, found: 414.2125.

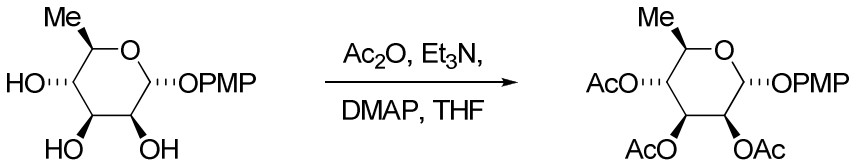


221 **222**

Glycal 222: In a dry flask glycal **221** (445.3 mg, 1.077 mmol) was added with Ac_2O (0.20 mL, 2.15 mmol), pyridine (0.17 mL, 2.15 mmol), and DMAP (13.1 mg, 0.11 mmol). After 2 h the reaction appeared complete and solvent was removed by *vacuo*. The crude reaction mixture was chromatographed (85:15, hexanes : EtOAc) to provide glycal **222** (418.5 mg, 85%)

$[\alpha]_D$ = -127.4 (*c* = 1.285, CH_2Cl_2); IR (neat) 3413, 2985, 2937, 2881, 1749, 1651, 1496, 1375, 1242, 1072 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.23 (d, J = 6.0 Hz, 1 H), 5.93 (ddd, J = 4.8, 10.4, 16.0 Hz, 1 H), 5.39 (s, 1 H), 5.31 (m, 2 H) 5.19 (dd, J = 1.6, 10.4 Hz, 1 H), 4.99 (dd, J = 7.6, 8.0 Hz, 1 H), 4.51 (d, J = 5.6 Hz, 2 H), 4.41 (d, J = 8.0 Hz, 1 H), 4.14 (dd, J = 5.2, 7.6 Hz, 1 H), 4.03 (dd, J = 2.0, 5.2 Hz, 1

H), 3.95 (dq, J = 6.4, 10.0 Hz, 1 H), 3.86 (dq, J = 2.0, 6.8 Hz, 1 H), 3.34 (d, J = 10.4 Hz, 1 H), 2.12 (s, 3 H), 1.60 (s, 3 H), 1.47 (s, 3 H), 1.40 (d, J = 6.8 Hz, 3 H), 1.36 (s, 3 H), 1.32 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 155.7, 142.3, 133.4, 117.7, 110.6, 105.8, 101.0, 83.7, 76.5, 73.3, 70.5, 69.4 (2 peaks), 65.3, 51.7, 28.0, 26.5, 25.2, 21.3, 17.4, 16.6; HRMS calcd for $C_{22}H_{34}NO_9$ $[M+H]^+$: 456.2228, found: 456.2231.

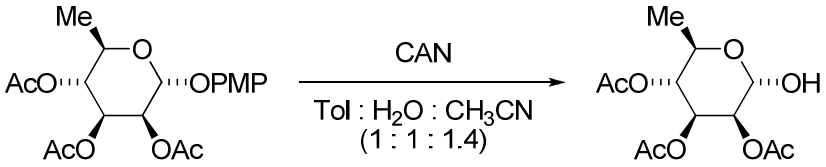


204 **234**

C1-(*p*-methoxyphenyl)-peracyl-D-rhamnose 234: Triol **204** (883.4 mg, 3.268 mmol) was taken up in dry THF (33.0 mL) at room temperature. Triethyl amine (4.15 mL, 29.7 mmol) was added, then Ac_2O (2.78 mL, 29.4 mmol), then DMAP (19.9 mg, 0.163 mmol), and the reaction mixture stirred for 30 min. The reaction mixture was then quenched into cold (ice bath) $NaHCO_3$ saturated solution (100 mL) and EtOAc (25 mL). The layers were separated and the aqueous phase was then extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4 and solvent removed by vacuo. The crude reaction mixture was then chromatographed (85:15 → 8:2, hexanes : EtOAc) to provide peracetylated product **234** (1.214 g, 94%) as a sticky residue.

$[\alpha]_D$ = +78.3 (*c* = 0.790, $CHCl_3$); IR (neat) 2984, 2939, 1749, 1509, 1220, 1040 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.01 (d, J = 9.2 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 5.50 (dd, J = 3.6, 10.4 Hz, 1 H), 5.42 (dd, J = 2.0, 3.6 Hz, 1 H), 5.34 (d, J = 1.6 Hz, 1 H), 5.15 (dd, J = 9.6, 10.4 Hz, 1 H), 4.03 (dq, J = 6.4 10.0 Hz, 1 H), 3.78 (s,

3 H), 2.19 (s, 3 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 1.21 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.3, 170.3, 155.4, 150.1, 117.8, 114.8, 96.6, 71.2, 70.0, 69.2, 67.2, 55.9, 21.2, 21.1, 21.0, 17.6; HRMS calcd for $C_{19}H_{24}O_9$ $[M+H]^+$: 397.1493, found: 397.1495.

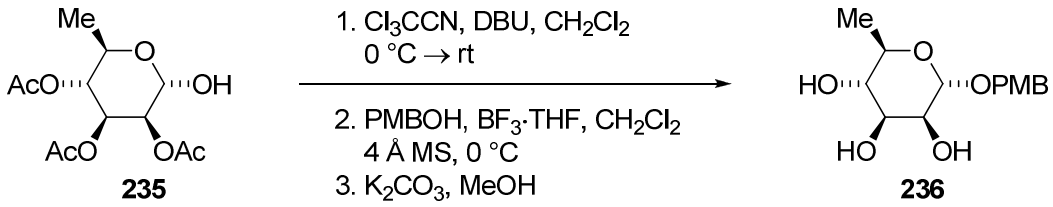


234 **235**

C2,C3,C4-acyl-D-rhamnose 235: Rhamnoside **234** (571.4 mg, 1.547 mmol) was taken up in acetonitrile (31.9 mL) and toluene (22.8 mL), and cooled to 0 °C (ice bath). CAN (8.480 g, 15.47 mmol) was taken up in H_2O (22.8 mL) and added dropwise to the reaction mixture over 3 minutes with strong stirring. After 1 h the reaction mixture was quenched into $NaHCO_3$ saturated solution (50 mL) and EtOAc (25 mL). The phases were separated, and the aqueous layer extracted with EtOAc (2 × 50 mL). The organic layers were combined, dried over Na_2SO_4, solvent removed by *vacuo*, and the crude mixture chromatographed (8:2, hexanes : EtOAc) to provide rhamnoside **235** (329.9 mg, 73%) as a mixture of anomers favoring the α-epimer.

α-epimer: IR (neat) 3475, 2983, 2927, 2854, 1747, 1373, 1225, 1053 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 5.37 (dd, J = 3.6, 10.0 Hz, 1 H), 5.28 (dd, J = 2.0, 3.6 Hz, 1 H), 5.17 (dd, J = 1.6, 4.0 Hz, 1 H), 5.09 (dd, J = 9.6, 10.4 Hz, 1 H), 4.14 (dq, J = 6.4, 10.0 Hz, 1 H), 3.11 (d, J = 4.4 Hz, 1 H), 2.16 (s, 3 H), 2.07 (s, 3 H), 2.00 (s, 3 H), 1.23 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.3, 170.3,

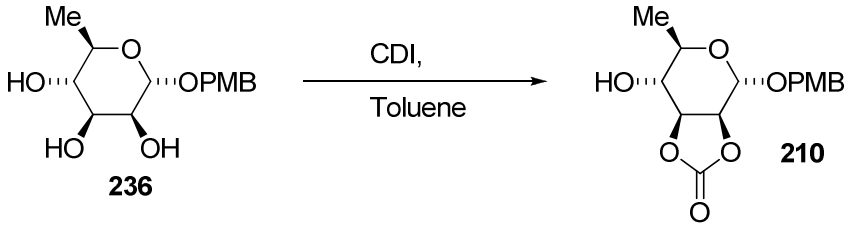
92.3, 71.3, 70.4, 68.9, 66.6, 21.2, 21.1, 21.0, 17.7; HRMS calcd for $C_{12}H_{17}O_7$ [M-OH]$^+$: 273.0969, found: 273.0964.



C1-(*p*-methoxybenzyl)-D-rhamnose 236: Rhamnoside **235** (329.0 mg, 1.133 mmol) was taken up in CH_2Cl_2 (11.3 mL), then DBU (0.05 mL, 0.34 mmol) was added. The reaction mixture then cooled to 0 ℃ (ice bath), and Cl_3CCN (0.34 mL, 3.4 mmol) was added dropwise over 5 minutes. The reaction stirred for 30 min, warmed to ambient temperature and stirred for 4h. The reaction mixture was then filtered through a short pad of celite with EtOAc, solvent removed by *vacuo*, and the crude imidate dried under high vacuum. The imidate was then azeotroped with toluene (×3) and then taken up in CH_2Cl_2 (11.3 mL) with activated 4 Å MS (1.65 g). The reaction mixture was cooled to 0 ℃ (ice bath) and PMBOH (0.28 mL, 2.27 mmol) was added, then BF_3·THF (0.01 mL, 0.11 mmol). After 3 h the reaction was quenched into $NaHCO_3$ saturated solution (15 mL) and EtOAc (15 mL). The phases were separated and the aqueous layer extracted with EtOAc (2 × 15 mL), the organic layers combined, dried over Na_2SO_4 and solvent removed by vacuo. The crude reaction was then chromatographed (85:15, hexanes : EtOAc) to provide 459.7 mg of the alpha product containing inseparable PMBOH. The crude material was taken up in MeOH (11.3 mL) and K_2CO_3 (39.1 mg, 0.28 mmol) was added. After 3 h the reaction was complete. Solvent was removed by *vacuo*, and the reaction mixture

chromatographed (8:2 → 9:1 → 1:0, EtOAc : hexanes) to provide alcohol **236** (203.0 mg, 63% over 3 steps).

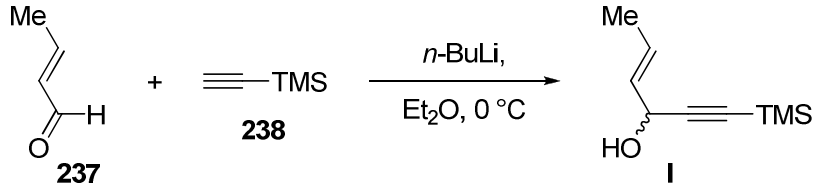
$[\alpha]_D$ = +75.7 (*c* = 0.885, CH_2Cl_2); IR (neat) 3369, 2931, 2837, 1514, 1250, 1049, 822 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 4.79 (app s, 1 H), 4.59 (d, J = 11.2 Hz, 1 H), 4.39 (d, J = 11.6 Hz, 1 H), 3.88 (app s, 1 H), 3.78 (s, 3 H), 3.75 (dd, J = 2.8, 8.8 Hz, 1 H), 3.68 – 3.63 (m, 2 H), 3.45 (dd, J = 9.2, 9.6 Hz, 1 H), 1.28 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 129.9, 129.3, 114.0, 98.9, 73.0, 71.9, 71.2, 69.0, 68.4, 55.5, 17.7.



Carbonate 210: In a dry round bottomed flask was added triol **236** (83.1 mg, 0.29 mmol) with carbonyl diimidazole (118.5 mg, 0.731 mmol) in toluene (5.8 mL) and the reaction stirred at ambient temperature. After 1.5 h the reaction appeared complete by TLC, and was quenched into $NaHCO_3$ saturated solution (20 mL) and EtOAc (15 mL). The layers were separated, and the aqueous phase extracted with EtOAc (2 × 15 mL), organic fractions combined, dried over Na_2SO_4, and solvent removed by *vacuo*. The crude reaction mixture was chromatographed to provide carbonate **210** (48.4 mg, 53%).

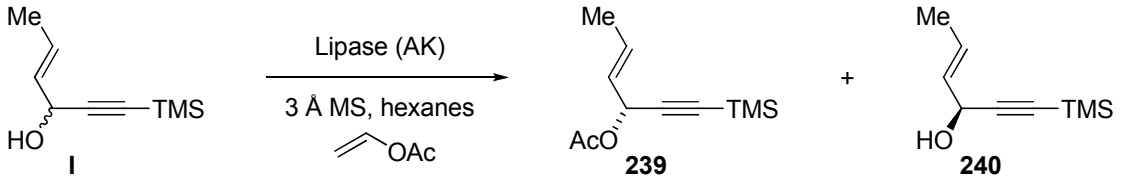
$[\alpha]_D$ = +77 (*c* = 0.20, CH_2Cl_2); IR (neat) 3450, 2418, 2848, 1815, 1516, 1174, 1070 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 5.09 (app s, 1 H), 4.70 (app t, J = 7.2 Hz, 1 H), 4.67 (d, J = 11.6 Hz, 1 H),

4.64 (app d, J = 6.8 Hz, 1 H), 4.48 (d, J = 11.2 Hz, 1 H), 3.84 (dq, J = 8.0, 6.0 Hz, 1 H), 3.82 (s, 3 H), 3.54 (app bt, 1 H), 3.19 (bs, 1 H), 1.35 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 153.9, 130.3, 128.1, 114.3, 94.1, 78.7, 76.3, 72.5, 69.6, 66.3, 55.5, 18.1; HRMS calcd for $C_{14}H_{17}O_4$ $[M - CO_3H]^+$: 249.1121, found: 249.1122, $C_{15}H_{17}O_6$ $[M\text{-}OH]^+$: 293.1020, found: 293.1021.

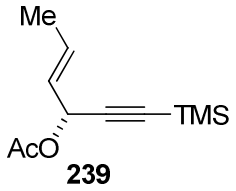


Propargylic alcohol I: Trimethylsilyl acetylene (12.4 mL, 85.6 mmol) was dissolved in Et_2O (118.8 mL) and cooled on an icebath under argon. *n*-BuLi (2.5 M in hexanes, 31.4 mL, 78.5 mmol) was then added dropwise over 1 hours and stirred an additional 30 min on icebath. Crotonaldehyde (5.91 mL, 71.3 mmol) was added dropwise over 30 min and the reaction stirred an additional 30 min. The reaction mixture was then quenched with NH_4Cl saturated solution (20 mL) added slowly. Water was added (10 mL), the layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 25 mL). The organic fractions were combined, dried over Na_2SO_4, and solvent removed by *vacuo* yielding ~12 g of crude allylic alcohol **I**. The crude reaction mixtre was carried on to enzymatic resolution without further purification.

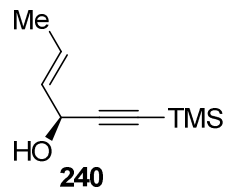
^{1}H (400 MHz, $CDCl_3$) δ 5.90 (app. sextet, J = 6.4 Hz, 1 H), 5.61 (m, 1 H), 4.82 (bs, 1 H), 1.87 (bs, 1 H), 1.75 (d, J = 6.4 Hz, 3 H), 0.19 (s, 9 H).



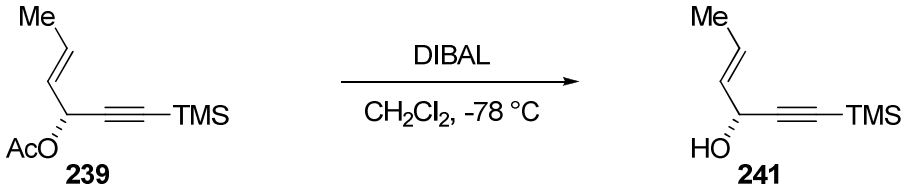
Propargylic ester 239 and alcohol 240: Allylic alcohol **I** (~12g, ~71.3 mmol) was taken up in hexanes (238 mL) at room temperature in a dry 500 mL round bottomed flask and 3 Å MS (activated, 13.4 g). Lipase (AK) (6 g) was added followed by vinyl acetate (26.3 mL, 285 mmol). The reaction as stirred for 18 h at ambient temperature, then filtered through a short pad of celite. Solvent was removed by *vacuo* and the crude reaction mixture chromatographed (95 : 5 hexanes : ethyl acetate) to provide allylic acetate **239** (7.65 g, 43%) and allylic alcohol **240** (5.62 g, 40%).



Propargylic ester 239: $[\alpha]_D$ = -4.1 (*c* = 0.750, CH_2Cl_2); IR (neat) 3037, 2960, 2181, 1747, 1371, 1228, 1016, 847 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.01 (ddq, J = 0.8, 6.4, 15.2 Hz, 1 H), 5.85 (dd, J = 0.8, 6.4 Hz, 1 H), 5.55 (ddq, J = 1.6, 6.8, 15.2 Hz, 1 H), 2.10 (s, 3 H), 1.76 (ddd, J = 0.8, 1.6, 6.8 Hz, 3 H), 0.20 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 132.0, 126.6, 101.1, 91.9, 64.8, 21.4, 17.8, 0.0; HMRS calcd for $C_9H_{15}Si$ $[M - OAc]^+$: 151.0938, found: 151.0937.



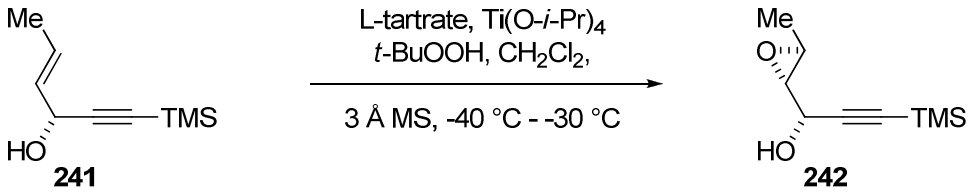
Propargylic alcohol 240: $[\alpha]_D$ = +63.4 (*c* = 0.410, CH_2Cl_2); IR (neat) 3329, 3030, 2962, 2918, 2173, 1250, 1024, 960, 845, 760 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 5.90 (ddq, J = 1.2, 6.4, 15.2 Hz, 1 H), 5.63 (dddq, J = 1.2, 4.8, 1.6, 14.8 Hz, 1 H), 4.82 (dd, J = 5.2, 5.2 Hz, 1 H), 1.83 (d, J = 5.6 Hz, 1 H), 1.75 (dd, J = 6.4, 1.2 Hz, 3 H), 0.19 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.1, 129.4, 104.9, 90.8, 63.6, 17.8, 0.1; HRMS calcd for $C_9H_{17}OSi$ $[M+H]^+$: 169.1043, found: 169.1042; Mosher ester analysis of the alcohol revealed >95:5 er.



Propargylic alcohol 241: In a dry 250 mL round bottomed flask at rt, under argon, was added allylic acetate **239** (6.411 g, 30.48 mmol) in CH_2Cl_2 (61 mL), and cooled to -78 °C. DIBAL-H (1.0 M in hexanes, 45.7 mL, 45.72 mmol) was then added over 30 min. The reaction was stirred for 1 h at -78 °C, then quenched with 65 mL Rochelle's salt saturated solution. The mixture was allowed to warm to rt and stirred until the reaction mixture was no longer cloudy. The layers were the separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 100 mL). The organic fractions were combined, dried over Na_2SO_4, solvent removed by *vacuo*, and chromatographed (9:1, hexanes : ethyl acetate) to provide allylic alcohol **241** (3.415 g, 67%) as a clear oil.

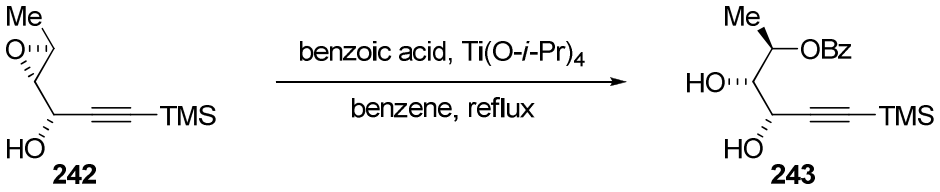
$[\alpha]_D$ = -56.1 (*c* = 0.420, CH_2Cl_2); IR (neat) 3334, 2962, 2918, 2858, 2171, 1259, 1024, 960, 845, 760 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 5.89 (ddq, 1.2, 6.4, 15.2 Hz, 1 H), 5.61 (ddq, 1.6, 6.4, 15.2 Hz, 1 H), 4.81 (dd, J = 6.0, 6.4 Hz, 1 H), 1.80 (dd, J

= 1.2, 6.0 Hz, 1), 1.73 (dd, J = 1.2, 6.8 Hz, 3 H), 0.18 (s, 9 H); HRMS calcd for $C_9H_{15}Si$ $[M\text{-}OH]^+$: 151.0938, found: 151.0931, calcd for $C_9H_{17}OSi$ $[M+H]^+$: 169.1043, found: 169.1036. Mosher ester analysis of the alcohol revealed >95:5 er.



Epoxide 242: In a 100 mL round bottomed flask, 3 Å MS (2 g) were activated, and placed under argon. CH_2Cl_2 (30 mL) was added, followed by L-tartrate (0.83 mL, 3.955 mmol), and the mixture cooled to -30 °C (± 5 °C) on an acetone bath. After 15 min, Ti(O-*i*-Pr)$_4$ (1.23 mL, 3.95 mmol) was added, the reaction stirred for 15 min, then *t*-BuOOH (3.95 mL, 21.8 mmol) was added slowly over 10 min. In a separate 50 mL round bottomed flask 3 Å MS (2 g) were activated and placed under argon. To this vessel, allylic alcohol **241** (3.328 g, 19.77 mmol) was added in CH_2Cl_2 (25 mL). The allylic alcohol solution was then added to the tartrate solution slowly over 3 h. The reaction was allowed to stir at -30 °C for 4 h, then placed in a -20 °C freezer, without stirring, for 10 h. The reaction was then treated with a solution of citric acid (0.760 g, 3.955 mmol) in acetone (55 mL) and stirred for 1 h. The reaction was then filtered through a pad of celite with CH_2Cl_2, and the solvent removed by *vacuo*. The crude mixture was then chromatographed (9:1 → 85:15, hexanes : ethyl acetate) to provide pure epoxy alcohol **242** (1.95 g, 53%) as a clear, sticky oil, along with a fraction of slightly impure **242** (803 mg, ~22% crude, estimated 70% total).

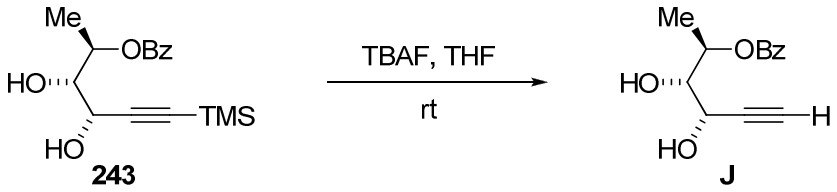
$[\alpha]_D$ = -4.1 (*c* = 0.750, CH_2Cl_2); IR (neat) 3402, 2960, 2924, 2852, 2175, 1252, 845 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 4.58 (dd, J = 3.6, 5.2 Hz, 1 H), 3.20 (dq, J = 2.0, 5.2 Hz, 1 H), 2.99 (dd, J = 2.4, 3.2 Hz, 1 H), 2.15 (d, J = 5.2 Hz, 1 H), 1.38 (d, J = 5.2 Hz, 3 H), 0.19 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.7, 91.9, 61.6, 60.5, 52.5, 17.2, 0.0; HRMS calcd for $C_9H_{15}OSi$ $[M-OH]^+$: 167.0887, found: 167.0885.



Diol 243: Expoxide **242** (1.94 g, 10.5 mmol) was dissolved in benzene (5.3 mL), followed by the addition of benzoic acid (2.96 mL, 11.6 mmol). The reaction mixture was heated to reflux and $Ti(O\text{-}i\text{-}Pr)_4$ (1.93 g, 15.8 mmol) was added. After stirring for 30 minutes at reflux, the reaction mixture was allowed to cool to rt and added to Et_2O (250 mL) in a 1 L flask. A 5% solution of H_2SO_4 (125 mL) was added slowly under strong stirring, to provide a white opaque mixture which was stirred until clear. The layers were then separated and the aqueous phase extracted with ethyl acetate (2 × 100 mL). The organic fractions were combined, dried over Na_2SO_4, solvent removed by *vacuo*, and the crude reaction mixture chromatographed to provide diol **243** (2.62 g, 81%) as a clear oil.

IR (neat) 3432, 2960, 2900, 2175, 1722, 1277, 1049, 845, 712 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 8.04 (m, 2 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.46 (m, 2 H), 5.22 (dq, J = 6.4, 6.8 Hz, 1 H), 4.61 (dd, J = 4.0, 7.6 Hz, 1 H), 3.88 (ddd, J = 3.6, 6.8, 7.2 Hz, 1 H), 2.57 (d, J = 7.6 Hz, 1 H), 2.37 (d, J = 7.6 Hz, 1 H), 1.51 (d, J = 6.8 Hz, 3 H),

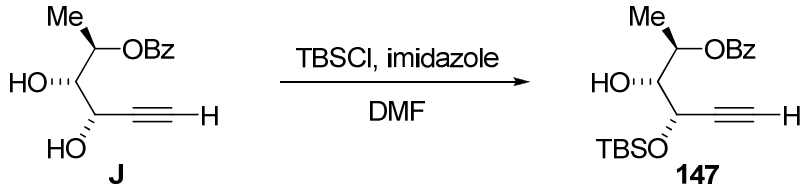
0.09 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 133.4, 130.4, 129.9, 128.6, 102.0, 93.1, 76.1, 71.8, 64.6, 16.8, 0.2; HRMS calcd for $C_{16}H_{23}O_4Si$ $[M+H]^+$: 307.1360, found: 307.1361.



Diol J: In a dry 100 mL round bottomed flask was added diol **243** (1.82 g, 5.94 mmol) in THF (60 mL) at rt under argon, and TBAF was added dropwise. After 2 h, the reaction appeared to be complete by TLC. The reaction mixture was poured into a strongly stirring solution of $NaHCO_3$ saturated solution (50 mL) and ethyl acetate (50 mL). The layers were separated, the aqueous phase extracted with ethyl acetate (3 × 50 mL), the organic fractions dried over Na_2SO_4, and solvent removed by *vacuo*. The crude reaction mixture was then chromatographed (85:15 → 7:3, hexanes : ethyl acetate) to provide diol **J** (622.5 mg, 45%) as a clear oil along with 719.3 mg of a slightly impure fraction. The impure fraction was rechromatographed to provide additional diol **J** (681.6 mg, 94% total).

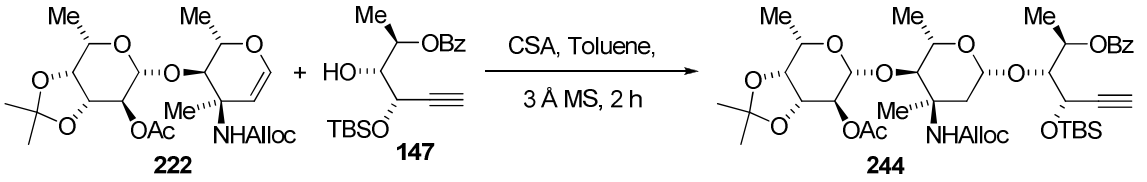
$[\alpha]_D$ = -63.9 (*c* = 0.505, CH_2Cl_2); IR (neat) 3421, 3296, 2985, 2926, 2115, 1709, 1279, 1117, 1051, 714 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 1.2, 7.2 Hz, 2 H), 7.59 (dt, J = 1.2, 7.2 Hz, 1 H), 7.46 (m, 2 H), 5.27 (app. quintet, J = 6.0 Hz, 1 H), 4.62 (m, 1 H), 3.93 (m, 1 H), 2.79 (d, J = 8.0 Hz, 1 H), 2.57 (d, J = 7.2 Hz, 1 H), 2.47 (d, J = 2.0 Hz, 1 H), 1.51 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 133.5, 130.2, 129.9, 128.6, 80.8, 76.1, 75.9, 71.6, 63.9, 16.8;

HRMS calcd for $C_{13}H_{14}O_4Na$ $[M+Na]^+$: 257.0784, found: 257.0782, calcd for $C_{13}H_{15}O_4$ $[M+H]^+$: 235.0965, found: 235.0964.

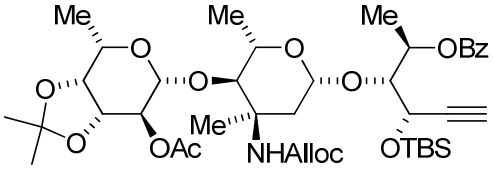


Silyl ether 147: Diol **J** (347.1 mg, 1.482 mmol) was added to a dry 25 mL round bottomed flask with imidazole (201.8 mg, 2.964 mmol) and DMF (14.8 mL). TBSCl (223.4 mg, 1.482 mmol) was next added and the reaction stirred at ambient temperature for 1 h. The crude reaction mixture was extracted with EtOAc (3 × 20 mL) and H_2O (20 mL), the organic layers combined, dried over Na_2SO_4, and solvent removed under reduced pressure. The mixture was then chromatographed (95 : 5 → 9 : 1, hexanes : EtOAc) to provide silyl ether **147** (375.6 mg, 73%) as a thick residue.

$[\alpha]_D$ = -51 (*c* = 0.283, CH_2Cl_2); IR (neat) 3500, 3307, 2954, 2931, 2858, 2115, 1718, 1277, 1111, 1070, 839, 712 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.6 Hz, 2 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.46 (m, 2 H), 5.34 (dq, J = 6.0, 6.4 Hz, 1 H), 4.57 (dd, J = 2.4, 4.8 Hz, 1 H), 3.89 (ddd, J = 4.4, 4.4, 6.4 Hz, 1 H), 2.60 (d, J = 4.4 Hz, 1 H), 2.47 (d, J = 2.0 Hz, 1 H), 1.47 (d, J = 6.4 Hz, 3 H), 0.94 (s, 9 H), 0.19 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.7, 133.2, 130.5, 129.8, 128.6, 81.3, 76.2, 75.3, 71.6, 64.6, 25.9, 18.4, 16.1, -4.2, -4.9; HRMS calcd for $C_{19}H_{29}O_4Si$ $[M+H]^+$: 349.1830, found: 349.1822.



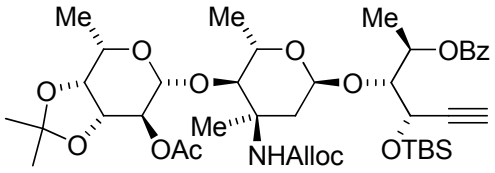
Glycoside 244: In a dry round bottomed flask was added glycal **222** (100.7 mg, 0.221 mmol) and alcohol **147** (231.1 mg, 0.663 mmol). The mixture was azeotroped with toluene (×3) to remove any residual water. Activated 3 Å MS (375 mg) and a stir bar were added, and placed under high vacuum for 1 h. Toluene (2.8 mL) was added, cooled to -5 °C (ice/brine bath), and camphor sulfonic acid (513.5 mg, 2.21 mmol) was added. After 1 h, more CSA (513.5 mg, 2.21 mmol) was added and stirred an additional hour. The reaction mixture was then quenched into $NaHCO_3$ saturated solution (7 mL) and EtOAc (10 mL). The phases were separated, and the aqueous layer extracted with EtOAc (2 × 15 mL), dried organic layers over Na_2SO_4, and removed solvent by *vacuo*. The crude reaction mixture was then chromatographed (1:0 → 9:1 → 85:15 → 7:3, hexanes : EtOAc) to provide β-glycoside **244** (145.7 mg, 82 %), and α-glycoside **K** (17.5 mg, 10%) and recovered **147** (150.4 mg).



244

β-Glycoside 244: $[\alpha]_D$ = -7.6 (*c* = 1.25, CH_2Cl_2); IR (neat) 3411, 2985, 2935, 2883, 2860, 1751, 1722, 1502, 1375, 1277, 1228, 1074 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 8.11 (app d, J = 6.8 Hz, 2 H), 7.54 (app t, J = 7.2 Hz, 1 H), 7.41 (app t, J = 8.0 Hz, 2 H), 5.92 (ddd, J = 5.2, 10.4, 17.2 Hz, 1 H), 5.37 (dq, J = 3.6, 6.8 Hz, 1

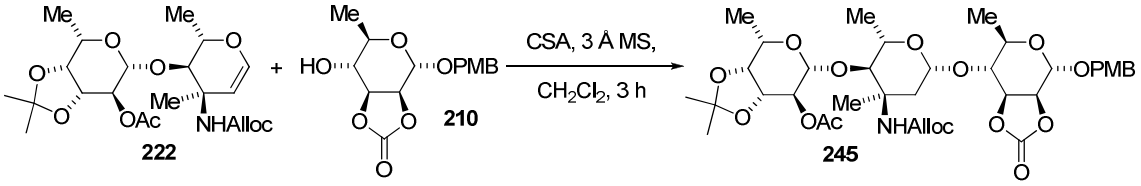
H), 5.31 (app d, J = 17.2 Hz, 1 H), 5.21 (app d, J = 10.4 H, 1 H), 5.00 (app d, J = 8.4 Hz, 1 H), 4.93 (m, 2 H), 4.47 (m, 2 H), 4.41 (dd, J = 2.4, 6.8 Hz, 1 H), 4.30 (d, J = 8.0 Hz, 1 H), 4.11 (dd, J = 5.2, 7.6 Hz, 1 H), 4.05 (dd, J = 3.6, 7.2 Hz, 1 H), 4.01 (dd, J = 2.4, 5.6 Hz, 1 H), 3.82 (dq, J = 2.0, 6.8 Hz, 1 H), 3.55 (dq, J = 6.4, 9.6 Hz, 1 H), 3.35 (app d, J = 12.8 Hz, 1 H), 3.07 (d, J = 9.6 Hz, 1 H), 2.44 (d, J = 2.0 Hz, 1 H), 2.08 (s, 3 H), 1.43 (m, 1 H), 1.42 (s, 3 H), 1.39 (d, J = 6.4 Hz, 3 H), 1.38 (s, 3 H), 1.36 (d, J = 6.4 Hz, 3 H), 1.35 (s, 3 H), 1.04 (d, J = 6.4 Hz, 3 H), 0.92 (s, 9 H), 0.17 (s, 3H), 0.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 166.0, 155.3, 133.3, 132.8, 131.0, 130.1, 128.2, 117.8, 110.5, 100.9, 99.3, 84.8, 82.8, 81.6, 77.6, 76.5, 75.0, 73.4, 70.5, 69.7, 69.4, 65.1, 63.7, 55.5, 39.3, 28.0, 26.5, 25.9, 25.1, 21.3, 18.2, 17.9, 16.6, 14.4, -4.2, -5.0; HRMS calcd for $C_{41}H_{62}NO_{13}Si$ $[M+H]^+$: 804.3990, found: 804.4023, calcd for $C_{41}H_{64}NO_{14}Si$ $[M+H_3O]^+$: 822.4096, 822.4117.



K

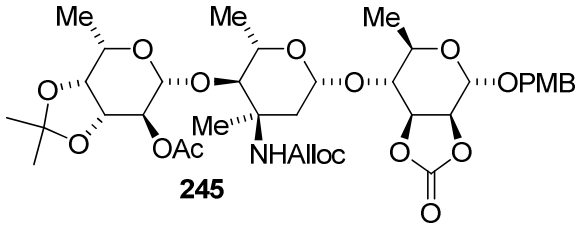
α-Glycoside K: $[\alpha]_D$ = -34.6 (*c* = 0.34, CH_2Cl_2); IR (neat) 3437, 2983, 2933, 2858, 2116, 1722, 1508, 1375, 1273, 1230, 1072 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.99 (m, 2 H), 7.55 (m, 1 H), 7.42 (m, 2 H), 5.94 (ddd, J = 5.6, 10.8, 17.2 Hz, 1 H), 5.55 (dq, J = 2.4, 6.8 Hz, 1 H), 5.32 (dd, J = 1.6, 17.2 Hz, 1 H), 5.25 (s, 1 H), 5.18 (dd, J = 1.6, 10.4 Hz, 1 H), 5.10 (app d, J = 3.2 Hz, 1 H), 4.98 (app t, J = 8.0 Hz, 1 H), 4.48 (m, 2 H), 4.36 (d, J = 8.0 Hz, 1 H), 4.27 (app d, J = 5.6 Hz, 1 H), 4.24 (dq, J = 6.0, 9.6 Hz, 1 H), 4.13 (dd, J = 5.6, 7.6 Hz, 1 H), 4.02 (dd, J = 2.0,

5.2 Hz, 1 H), 3.97 (dd, J = 2.4, 7.2 Hz, 1 H), 3.84 (dq, J = 1.6, 6.4 Hz, 1 H), 3.34 (app d, J = 14.8 Hz, 1 H), 3.12 (d, J = 9.2 Hz, 1 H), 2.43 (d, J = 2.0 Hz, 1 H), 2.10 (s, 3 H), 1.60 (s, 3 H), 1.45 (s, 3 H), 1.40 (d, J = 6.8 Hz, 3 H), 1.36 (s, 3 H), 1.31 (d, J = 6.4 Hz, 3 H), 1.22 (d, J = 6.4 Hz, 3 H), 0.92 (s, 9 H), 0.18 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 165.7, 155.2, 133.8, 133.0, 130.7, 129.8, 128.5, 117.3, 110.5, 101.2, 97.7, 85.4, 84.2, 81.6, 77.6, 76.5, 73.9, 73.5, 72.0, 69.3, 64.9, 64.1, 63.9, 53.0, 36.9, 29.9, 28.0, 26.5, 25.9, 21.3, 18.3, 18.0, 16.6, 13.8, -4.1, -5.0; HRMS calcd for $C_{41}H_{62}NO_{13}Si$ $[M+H]^+$: 804.3985, found: 804.3985.



Glycoside 245: In a dry vial was added glycal **222** (23.7 mg, 0.052 mmol) with rhamnoside **210** (48.4 mg, 0.156 mmol) and the mixture azeotroped with toluene (3 × 25 mL). A stir bar and freshly activated 3 Å MS (100 mg) were added, and the mixture placed under high vacuum for 3 h. To the reaction mixture was added CH_2Cl_2 (0.65 mL) and the reaction cooled to -5 °C (ice/brine bath). Camphor sulfonic acid (120.8 mg, 0.520 mmol) was added and th reaction was stirred for 1 h. Additional CSA was added (120.8 mg, 0.520 mmol) and the reaction stirred for 2 h. The mixture was quenched in $NaHCO_3$ saturated solution (10 mL) and EtOAc (10 mL) under vigorous stirring, and the layers separated. The aqueous phase was extracted with EtOAc (3 × 10 mL), the organic fractions combined, and washed with $NaHCO_3$ saturated solution (10 mL). The organic

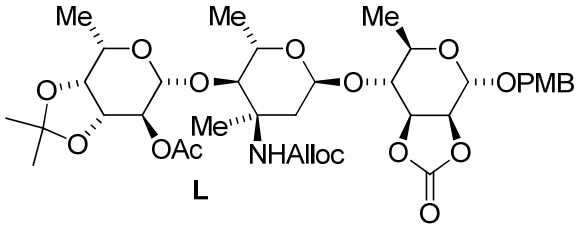
phase was then dried over Na_2SO_4, and solvent removed by vacuo. The crude reaction mixture was chromatographed (9:1 → 85:15 → 8:2 → 7:3 → 6:4, hexanes : EtOAc) to provide recovered **210** (22.5 mg), β-glycoside **245** (23.5 mg, 59%), and α-glycoside **L** (13.5 mg, 34%).



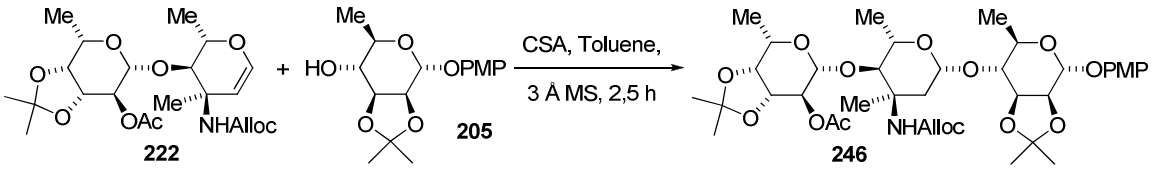
245

β-glycoside 245: $[\alpha]_D$ = +27.1 (*c* = 0.40, CH_2Cl_2); IR (neat) 3411, 2985, 2935, 2879, 1819, 1749, 1726, 1504, 1375, 1230, 1128, 1072, 732 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 5.94 (ddd, J = 5.6, 10.8, 17.2 Hz, 1 H), 5.32 (dd, J = 1.6, 17.2 Hz, 1 H), 5.22 (dd, J = 1.2, 10.4 Hz, 1 H), 5.07 (app s, 1 H), 4.99 (s, 1 H), 4.96 (app t, J = 8.0 Hz, 1 H), 4.86 (dd, J = 1.2, 9.2 Hz, 1 H), 4.75 (app t, J = 7.2 Hz, 1 H), 4.62 (d, J = 11.2 Hz, 1 H), 4.60 – 4.57 (m, 1 H), 4.57-4.50 (m, 3 H), 4.44 (d, J = 11.2 Hz, 1 H), 4.35 (d, J = 8.0 Hz, 1 H), 4.14 (dd, J = 5.6, 7.6 Hz, 1 H), 4.02 (dd, J = 2.4, 5.6 Hz, 1 H), 3.83 (dq, J = 6.8, 2.4 Hz, 1 H), 3.82 (s, 3 H), 3.75 (dq, J = 6.0, 9.6 Hz, 1 H), 3.67 (dq, J = 6.8, 9.6 Hz, 1 H), 3.31 (app d, J = 13.6 Hz, 1 H), 3.10 (d, J = 10.0 Hz, 1 H), 2.13 (s, 3 H), 1.59 (s, 3 H), 1.41 (s, 3 H), 1.39 (d, J = 6.8 Hz, 3 H), 1.36 (s, 3 H), 1.32 (m, 1 H), 1.30 (d, J = 6.4 Hz, 3 H), 1.27 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 159.9, 155.6, 153.8, 133.2, 130.2, 128.4, 117.8, 114.2, 110.5, 100.9, 96.8, 93.9, 84.4, 79.5, 77.2 (overlap with $CDCl_3$ overlap), 76.8 ($CDCl_3$ overlap), 76.7, 76.5, 73.3, 69.8, 69.4, 69.2, 65.4, 63.6, 55.5, 55.4, 39.6, 28.0,

26.5, 25.4, 21.3, 18.1, 17.9, 16.6; HRMS calcd for $C_{37}H_{51}NO_{16}K$ $[M+K]^+$: 804.2839, found: 804.2839.



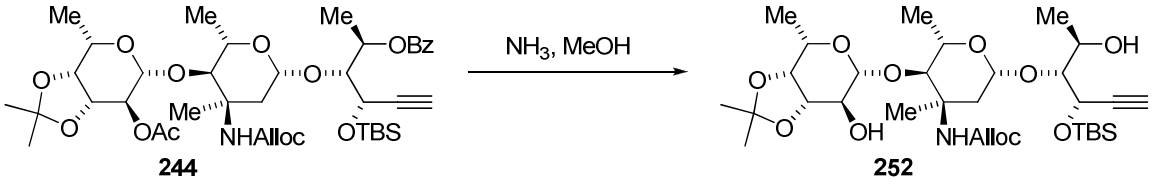
α-glycoside L: $[\alpha]_D$ = -44.3 (*c* = 0.315, CH_2Cl_2); IR (neat) 3429, 2983, 2929, 2877, 2854, 1817, 1747, 1726, 1514, 1238, 1070 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.4 Hz, 2 H), 6.90 (d, J = 8.8 Hz, 2 H), 5.88 (ddd, J = 5.6, 10.8, 17.2 Hz, 1 H), 5.24 (app d, J = 17.2 Hz, 1 H), 5.15 (s, 1 H), 5.09 (app d, J = 10.4 Hz, 1 H), 5.07 (app s, 1 H), 4.97 (app t, J = 8.0 Hz, 1 H), 4.82 (app d, J = 3.2 Hz, 1 H), 4.61 (d, J = 11.6 Hz, 1 H), 4.59 (m, 2 H), 4.54 (dd, J = 6.0, 13.0 Hz, 1 H), 4.44 (d, J = 11.2 Hz, 1 H), 4.37 (m, 1 H), 4.37 (d, J = 8.4 Hz, 1 H), 4.14 (dd, J = 5.2, 7.6 Hz, 1 H), 4.03 (dd, J = 2.4, 5.6 Hz, 1 H), 3.99 (dq, J = 6.4, 8.4 Hz, 1 H), 3.85 (dq, J = 2.0, 6.4 Hz, 1 H), 3.82 (s, 3 H), 3.73 (dq, J = 6.4, 10.4 Hz, 1 H), 3.42 (dd, J = 7.2, 10.4 Hz, 1 H), 3.29 (app d, J = 14.2 Hz, 1 H), 3.14 (d, J = 9.6 Hz, 1 H), 2.14 (s, 3 H), 1.59 (s, 3 H), 1.56 (dd, J = 4.4, 14.8 Hz, 1 H), 1.42 (s, 3 H), 1.40 (d, J = 6.4 Hz, 3 H), 1.36 (s, 3 H), 1.30 (d, J = 6.4 Hz, 3 H), 1.27 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 159.9, 155.2, 153.7, 133.7, 130.3, 128.3, 117.7, 114.2, 110.5, 101.1, 97.7, 93.9, 84.8, 78.4, 78.3, 78.0, 77.3, 76.5, 73.3, 69.3, 69.2, 64.9, 64.5, 64.4, 55.5, 53.0, 36.2, 28.0, 26.5, 25.7, 21.3, 17.6, 17.6, 16.6; HRMS calcd for $C_{37}H_{51}NNaO_{16}$ $[M+Na]^+$: 788.3100, found: 788.3101.



Glycoside 246: In a dry vial was added glycal **222** (14.2 mg, 0.031 mmol) with rhamnoside **205** (21.7 mg, 0.070 mmol) and the mixture azeotroped with toluene (3 × 5 mL). A stir bar and freshly activated 3 Å MS (56.8 mg) were added, and the mixture placed under high vacuum for 2 h. To the reaction mixture was added toluene (0.6 mL) and the reaction cooled to -5 °C (ice/brine bath). Camphor sulfonic acid (72.0 mg, 0.310 mmol) was added and the reaction was stirred for 1 h. Additional CSA was added (72.0 mg, 0.310 mmol) and the reaction stirred for 1.5 h. The mixture was quenched in $NaHCO_3$ saturated solution (15 mL) and EtOAc (15 mL) under vigorous stirring, and the layers separated. The aqueous phase was extracted with EtOAc (3 × 20 mL), the organic fractions combined, and washed with $NaHCO_3$ saturated solution (20 mL). The organic phase was then dried over Na_2SO_4, and solvent removed by vacuo. The crude reaction mixture was chromatographed (1:0 → 9:1 → 85:15 → 8:2, hexanes : EtOAc) to provide β-glycoside **246** (21.5 mg, 90%).

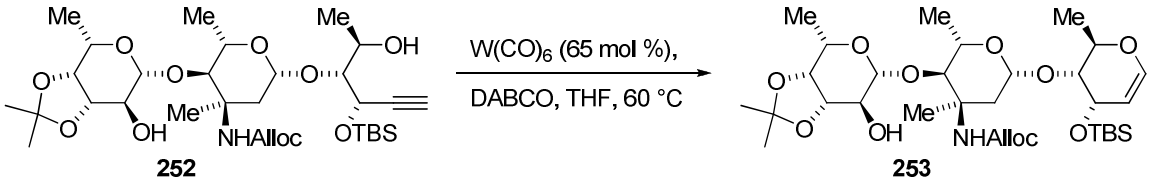
$[\alpha]_D$ = +254 (*c* = 0.091, CH_2Cl_2); IR (neat) 3410, 2981, 2927, 2858, 1728, 1508, 1377, 1223, 1072, 1041 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.98 (d, J = 8.8 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 2 H), 5.96 (ddd, J = 5.0, 10.8, 17.2 Hz, 1 H), 5.57 (app s, 1 H), 5.33 (dd, J = 1.2, 17.2 Hz, 1 H), 5.22 (app d, J = 10.4 Hz, 1 H), 5.03 (app d, J = 9.2 Hz, 1 H), 4.99 (s, 1 H), 4.96 (app t, J = 8.0 Hz, 1 H), 4.56 (dd, J = 5.6, 13.2 Hz, 1 H), 4.55 (dd, J = 5.2, 13.6 Hz, 1 H), 4.35 (d, J = 8.0 Hz, 1 H), 4.29 (m, 1 H), 4.28 (m, 1 H), 4.13 (dd, J = 5.2, 6.8 Hz, 1 H), 4.02 (dd, J = 2.0, 5.2 Hz, 1 H), 3.82

(dq, J = 2.0, 6.8 Hz, 1 H), 3.77 (s, 3 H), 3.76 (dq, J = 6.0 Hz, 1 H), 3.65 (dd, J = 6.8, 10.0 Hz, 1 H), 3.61 (dq, J = 9.6, 6.4 Hz, 1 H), 3.30 (app d, J = 13.2 Hz, 1 H), 3.10 (d, J = 9.6 Hz, 1 H), 2.12 (s, 3 H), 1.59 (s, 3 H), 1.54 (s, 3 H), 1.42 (s, 3 H), 1.39 (d, J = 6.0 Hz, 3 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.32 (dd, J = 10.0, 14.0 Hz, 1 H), 1.26 (d, J = 5.6 Hz, 3 H), 1.20 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 155.3, 155.0, 150.4, 133.4, 117.9, 117.7, 114.7, 110.5, 109.5, 101.1, 97.0, 96.3, 85.2, 85.1, 78.3, 76.5, 76.2, 73.4, 73.3, 69.7, 69.3, 65.5, 65.3, 55.8, 55.5, 39.8, 29.9, 28.0, 26.7, 26.5, 25.4, 21.3, 18.1, 17.8, 16.5; HRMS calcd for $C_{38}H_{55}NNaO_{15}$ $[M+Na]^+$: 788.34639, found: 788.3468.



Glycoside 252: In a 10 mL round bottomed flask was placed oligosaccharide **244** (144.7 mg, 0.180 mmol) in MeOH (10 mL). Ammonia was bubbled through solution for 1 h, the reaction was sealed with an ammonia atmosphere, and stirred for 24 h. Deacetylation was complete within 6 h, and removal of the benzoate was slow. Every 24 h, the reaction was checked for completion, then re-exposed to ammonia and sealed. After 7 d, solvent was removed by *vacuo*, then chromatographed (8:2, hexanes : EtOAc) to provide diol **252** (87.7 mg, 74%). Some material with the benzoate remaining was obtained, re-exposed to reaction conditions for 5 days, and chromatographed, producing more diol **252** (11.6 mg, 10%; total of 99.3 mg, 84%).

$[\alpha]_D$ = +4.8 (*c* = 2.815, CH_2Cl_2); IR (neat) 3415, 3307, 2983, 2935, 2885, 2860, 2117, 1728, 1502, 1381, 1248, 1072, 1041, 841, 735 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 5.90 (ddd, J = 5.6, 10.8, 17.2 Hz, 1 H), 5.30 (dd, J = 1.6, 17.2 Hz, 1 H), 5.22 (dd, J = 1.6, 10.4 Hz, 1 H), 5.01 (s, 1 H), 4.85 (s, 1 H), 4.81 (dd, J = 1.6, 9.2 Hz, 1 H), 4.48 (m, 2 H), 4.23 (d, J = 8.0 Hz, 1 H), 4.19 (dd, J = 2.0, 9.2 Hz, 1 H), 4.05 – 3.98 (m, 2 H), 3.96 (dq, J = 2.4, 6.8 Hz, 1 H), 3.85 – 3.77 (m, 2 H), 3.74 (dd, J = 2.8, 9.2 Hz, 1 H), 3.52 (dd, J = 6.8, 7.6 Hz, 1 H), 3.41 (app d, J = 13.2 Hz, 1 H), 3.19 (d, J = 10.0, 1 H), 2.44 (d, J = 1.6 Hz, 1 H), 1.55 (s, 3 H), 1.42 (s, 3 H), 1.40 (m, 1 H), 1.37 (d, J = 6.8 Hz, 3 H), 1.36 (s, 3 H), 1.35 (d, J = 6.0 Hz, 3 H), 1.09 (d, J = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.16 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 133.1, 118.1, 110.2, 102.7, 100.4, 87.5, 84.2, 83.3, 79.3, 76.4, 74.2, 73.9, 70.1, 69.5, 65.9, 65.3, 63.7, 55.6, 39.0, 28.5, 26.4, 25.8, 25.1, 18.5, 18.1, 16.7, 16.6, -4.2, -5.2; HRMS calcd for $C_{32}H_{56}NO_{11}Si$ $[M+H]^+$: 658.3617, found: 658.3626.

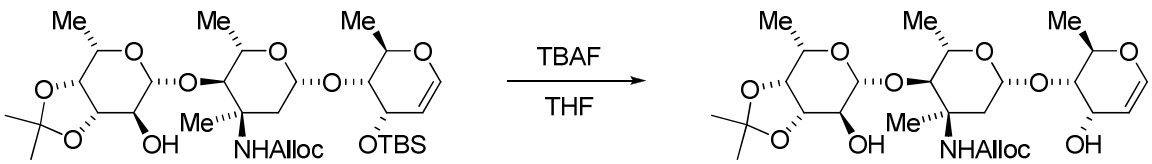


252 **253**

Glycal 253: In a dry 10 mL round bottomed flask was added alkyne alcohol **252** (87.7 mg, 0.13 mmol) in THF (3.0 mL) with $W(CO)_6$ (30.6 mg, 0.09 mmol) and DABCO (29.8 mg, 0.27 mmol), and exposed to hν (350 nm) at 60 °C. After 5 h, the reaction appears to have stalled, additional $W(CO)_6$ (21.1 mg, 0.06 mmol) and DABCO (14.9 mg, 0.13 mmol) were added, and the reaction re-exposed to hν. After an additional 5 h, only trace starting material remained. The reaction

was filtered through celite with EtOAc (10 mL), solvent removed by vacuo, and the crude material taken up in benzene (15 mL) and stored at -40 °C for 9 h. The benzene was then melted and removed by vacuo, and the crude reaction mixture chromatographed (85:15 → 8:2 → 7:3, hexanes : EtOAc) to provide glycal **253** (59.3 mg, 68%) along with exo-product (9.7 mg, 11%) and some recovered starting material (5.6 mg, 6%).

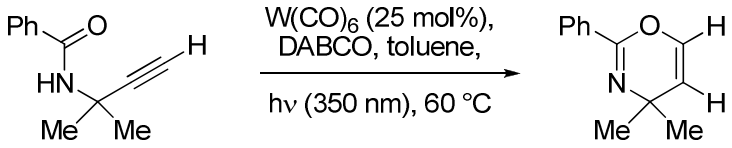
$[\alpha]_D$ = +94.0 (*c* = 0.885, CH_2Cl_2); IR (neat) 3423, 2983, 2933, 2881, 2858, 1730, 1502, 1379, 1072, 1039 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.29 (d, J = 6.0 Hz, 1 H), 5.92 (ddd, J = 5.6, 10.4, 17.2 Hz, 1 H), 5.30 (dd, J = 1.6, 17.2 Hz, 1 H), 5.22 (dd, J = 1.2, 10.0 Hz, 1 H), 5.04 (s, 1 H), 4.76 (m, 2 H), 4.49 (m, 2 H), 4.24 (d, J = 8.8 Hz, 1 H), 4.17 (dd, J = 3.2, 5.2 Hz, 1 H), 4.14 (dq, J = 6.4, 9.6 Hz, 1 H), 4.03 (m, 1 H), 3.99 (dd, j = 2.0, 5.2 Hz, 1 H), 3.81 (dq, J = 2.0, 6.4 Hz, 1 H), 3.69 (dq, J = 6.4, 9.6 Hz, 1 H), 3.65 (dd, J = 3.6, 10.0 Hz, 1 H), 3.52 (app t, J = 8.0 Hz, 1 H), 3.40 (app d, J = 13.6 Hz, 1 H), 3.20 (d, J = 10.0 Hz, 1 H), 2.54 (bs, 1 H), 1.55 (s, 3 H), 1.43 (s, 3 H), 1.39 (m, 1 H), 1.37 (d, J = 6.4 Hz, 3 H), 1.36 (s, 3 H), 1.32 (d, J = 6.8 Hz, 3 H), 1.30 (d, J = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 145.3, 133.1, 118.2, 110.2, 102.6, 102.1, 95.6, 84.5, 79.3, 76.5, 76.3, 74.0, 69.8, 69.7, 69.5, 65.4, 60.9, 55.6, 39.6, 28.5, 26.5, 26.1, 25.2, 18.6, 18.3, 17.9, 16.6, -3.9, -4.4; HRMS calcd for $C_{32}H_{55}NNaO_{11}Si$ $[M+Na]^+$: 680.3437, found: 680.3441.



253 **254**

Glycal 254: In a dry 5 mL round bottomed flask was added silyl ether **253** (21.6 mg, 0.033 mmol) in THF (2.0 mL). TBAF (0.16 mL, 0.16 mmol) was added in one portion and the reaction stirred at ambient temperature. The deprotection was slow taking 4 d to complete by TLC. The reaction mixture was quenched into $NaHCO_3$ saturated solution (7 mL) and EtOAc (10 mL). The layers were separated, the aqueous phase extracted with EtOAc (2 × 10 mL), the organic layers combined, dried over Na_2SO_4, and solvent removed under reduced pressure. The crude reaction mixture was chromatographed by prep-TLC using 1:1, hexanes : EtOAc to provide glycal **254** (16.7 mg, 94%) as a clear residue. $[\alpha]_D$ = +52.9 (*c* = 0.325, CH_2Cl_2); IR (neat) 3413, 2981, 2927, 2877, 1712, 1647, 1512, 1377, 1238, 1072 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.38 (d, J = 6.0 Hz, 1 H), 5.90 (ddd, J = 5.6, 10.4, 17.2 Hz, 1 H), 5.30 (dd, J = 1.6, 17.2 Hz, 1 H), 5.22 (dd, J = 1.6, 10.8 Hz, 1 H), 5.03 (s, 1 H), 4.86 (app t, J = 5.2 Hz, 1 H), 4.79 (dd, J = 1.6, 10.0 Hz, 1 H), 4.50 (m, 2 H), 4.21 (d, J = 8.4 Hz, 1 H), 4.17 (app s, 1 H), 4.06 (dq, J = 6.4, 9.2 Hz, 1 H), 4.00 (m, 1 H), 3.98 (dd, J = 2.4, 5.6 Hz, 1 H), 3.80 (dq, J = 2.0, 6.4 Hz, 1 H), 3.71 (dq, J = 6.0, 9.6 Hz, 1 H), 3.67 (dd, J = 3.6, 9.2 Hz, 1 H), 3.51 (app t, J = 8.4 Hz, 1 H), 4.25 (app d, J = 13.6 Hz, 1 H), 3.15 (d, J = 9.6 Hz, 1 H), 2.61 (bs, 1 H), 2.36 (bs, 1 H), 1.53 (s, 3 H), 1.45 (dd, J = 9.6, 14.0 Hz, 1 H), 1.39 (s, 3 H), 1.35 (d, J = 6.4 Hz, 3 H), 1.34 (s, 3 H), 1.31 (d, J = 6.4 Hz, 3 H), 1.29 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 146.5, 133.0, 118.3, 110.2, 102.7, 100.3, 96.7, 84.5, 79.2, 76.4, 74.0, 70.3, 69.7, 69.6, 65.6, 60.4, 55.8, 39.5, 28.5, 26.5, 25.7, 19.3, 18.5, 17.5, 16.6; HRMS calcd for $C_{26}H_{41}NNaO_{11}$ $[M+Na]^+$: 566.2572, found: 566.2583.

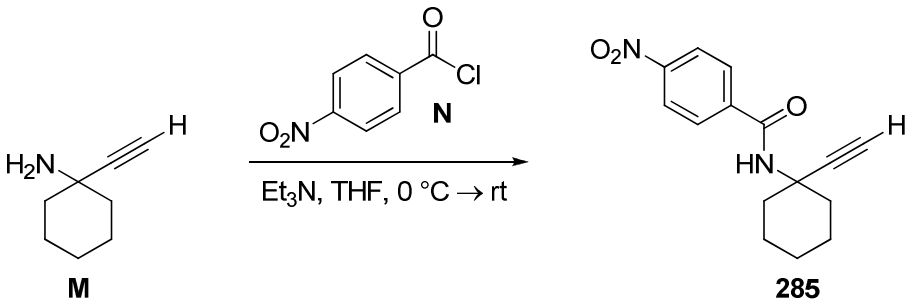
3.1.4. Experimental procedures of section 2.3



280 **281**

Oxazine 281: In a dry round bottomed flask was added amide **280** (75.0 mg, 0.40 mmol) with DABCO (89.9 mg, 0.80 mmol), $W(CO)_6$ (35.2 mg, 0.10 mmol) and toluene (6.5 mL). The reaction vessel was fitted with a dry condensing coil and exposed to hν (350 nm) at 60 °C for 2.5 h. The crude mixture was then filtered through a pad of celite with EtOAc, solvent removed under reduced pressure, and the crude mixture chromatographed (98:2, hexanes : EtOAc) to provide oxazine **281** (49.8 mg, 65%) a clear residue.

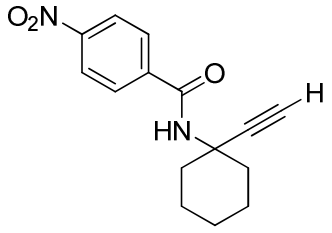
IR (neat) 3064, 2970, 1292, 1188, 1057 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.94 (app dd, J = 1.2, 8.4 Hz, 2 H), 7.37-7.44 (m, 3 H), 6.53 (d, J = 6.4 Hz, 1 H), 5.02 (d, J = 6.4, 1 H), 1.34 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 137.4, 133.0, 128.3, 127.5, 111.7, 49.7, 32.9; HRMS calcd for $C_{12}H_{14}NO$ $[M+H]^+$: 188.1070, found: 188.1070.



M **285**

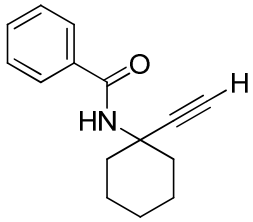
Representative Propargylic Amide Procedure: In a dry round bottomed flask was added amine **M** (0.15 mL, 1.11 mmol) in THF (3.0 mL) under argon, and the reaction mixture cooled on icebath. Acid chloride **N** (246.8 mg, 1.33 mmol) was

added dropwise followed by Et_3N (0.23 mL, 1.67 mmol). The reaction was then allowed to warm slowly to room temperature over 1.5 h, and the reaction stirred overnight for 11 h. The reaction was quenched into $NaHCO_3$ saturated solution (15 mL) and EtOAc (15 mL), the layers separated, and the aqueous phase extracted with EtOAc (2 × 15 mL). The organic layers were combined, dried over Na_2SO_4, and solvent removed under reduced pressure. The crude material was then chromatographed (8:2, hexanes : EtOAc) to provide amide **285** (252.1 mg, 83%) as a white solid.



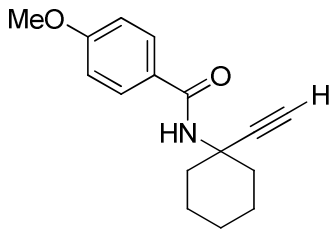
285

Amide 285: (252.1 mg, 83%); m.p. = 130 °C – 131 °C; IR (neat) 3298, 2935, 2860, 1651, 1525, 1348 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.2 Hz, 2 H), 7.90 (d, J = 7.2 Hz, 2 H), 6.45 (bs, 1 H), 2.47 (s, 1 H), 2.25 (m, 2 H), 1.87 (m, 2 H), 1.25 – 1.59 (m, 5 H), 1.29 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 149.5, 140.7, 128.4, 123.8, 84.9, 72.2, 52.7, 37.0, 25.3, 22.6; HRMS calcd for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: 273.1239, found: 273.1234.



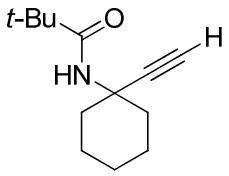
O

Amide O: (251.0 mg, 99%); m.p. = 131 °C – 132 °C; IR (neat) 3300, 2933, 2858, 1639, 1533, 1491, 1309 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.76 (m, 2 H), 7.48 (m, 1 H), 7.42 (m, 2 H), 6.16 (s, 1 H), 2.46 (s, 1 H), 2.24 (m, 2 H), 1.94 (m, 2 H), 1.77 – 1.59 (m, 5 H), 1.34 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 135.2, 131.6, 128.7, 127.1, 85.6, 71.7, 52.2, 37.1, 25.4, 22.7; HRMS calcd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1383, found: 228.381.



P

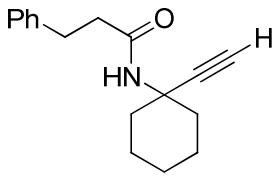
Amide P: (586.3 mg, 93%); m.p. = 110 °C – 112 °C; IR (neat) 3298, 2931, 2858, 1643, 1608, 1500, 1254, 1176 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.74 (d, J = 6.8 Hz, 2 H), 6.92 (d, J = 6.4 Hz, 2 H), 6.02 (s, 1 H), 3.85 (s, 3 H), 2.46 (s, 1 H), 2.26 – 2.22 (m, 2 H), 1.98 – 1.91 (m, 2 H), 1.78 – 1.59 (m, 5 H), 1.38 – 1.32 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.4, 128.9, 127.5, 113.9, 85.9, 71.6, 55.6, 52.1, 37.2, 25.5, 22.7; HRMS calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1494, found: 258.1489.



Q

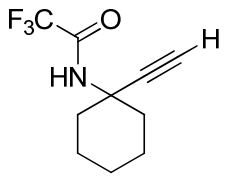
Amide Q: (483.7 mg, 95%); m.p. = 98 °C – 99 °C; IR (neat) 3390, 3240, 2931, 2858, 2102, 1643, 1520 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 5.56 (s, 1 H), 2.38 (s, 1 H), 2.08 – 2.05 (m, 2 H), 1.90 – 1.83 (m, 2 H), 1.71 – 1.62 (m, 2 H), 1.61 – 1.55 (m, 3

H), 1.32 – 1.29 (m, 1 H), 1.20 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 86.1, 71.1, 51.5, 39.3, 36.9, 27.8, 25.4, 22.7; HRMS calcd for $C_{13}H_{22}NO$ $[M+H]^+$: 208.1696, found: 208.1696.



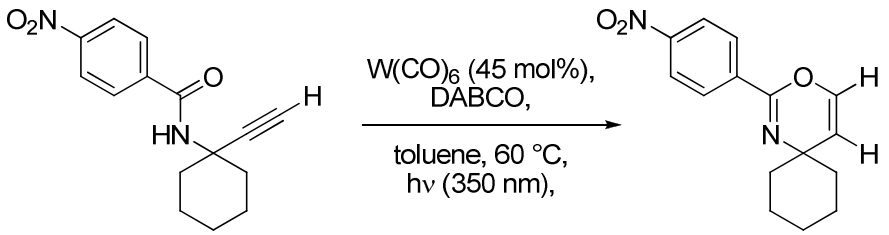
R

Amide R: (601.0 mg, 96%); m.p. = 152 °C – 153 °C; IR (neat) 3325, 3221, 2935, 2854, 2102, 1643, 1539, 698 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2 H), 7.22 – 7.20 (m, 3 H), 5.28 (s, 1 H), 2.97 (t, J = 7.2 Hz, 2 H), 2.46 (t, J = 7.6 Hz, 2 H), 2.40 (s, 1 H), 2.09 – 2.03 (m, 2 H), 1.74 – 1.50 (m, 7 H), 1.27 – 1.19 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 141.1, 128.7, 128.7, 126.4, 85.7, 71.5, 51.9, 39.3, 37.0, 31.8, 25.4, 22.6; HRMS calcd for $C_{17}H_{22}NO$ $[M+H]^+$: 256.1696, found: 256.1697.



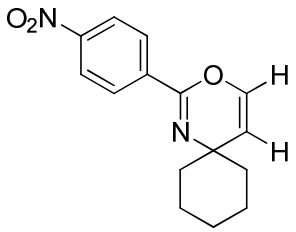
S

Amide S: (CF_3CO_2Me was used instead of the acid chloride, 811.2 mg, 45%); IR (neat) 3329, 3278, 2941, 2862, 1705, 1552, 1190, 1159 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 6.21(s, 1 H), 2.50 (s, 1 H), 2.18 – 2.15 (m, 2 H), 1.90 – 1.84 (m, 2 H), 1.75 – 1.62 (m, 5 H), 1.34 – 1.28 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.6, 117.1, 114.2, 83.4, 73.2, 53.3, 36.4, 25.1, 22.6; HRMS calcd for $C_{10}H_{13}F_3NO$ $[M+H]^+$: 220.0944, found 220.0944.



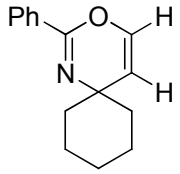
285 **286**

Representative Oxazine Cycloisomerization Procedure: In a dry round bottomed flask was added amide **285** (40.8 mg, 0.150 mmol) with DABCO (33.6 mg, 0.300 mmol) and $W(CO)_6$ (23.6 mg, 0.067 mmol) in toluene (3.0 Ml) under argon. The reaction vessel was fitted with a dry condensing coil and the mixture exposed to hν (350 nm) at 60 °C. After 3.5 the reaction appears complete by TLC. The crude reaction mixture was filtered through a pad of celite with EtOAc, then solvent removed under reduced pressure. The reaction mixture was then chromatographed (1:0 → 98:2 → 95:5 → 9:1, hexanes : EtOAc) to provide oxazine **286** (33.7 mg, 83%) as a clear residue.



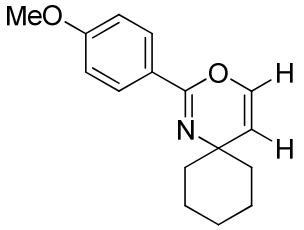
286

Oxazine 286: (33.7 mg, 83%); IR (neat) 2931, 2856, 1525, 1603, 1348, 1217, 1065, 866, 704 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 8.24 (d, J = 9.6 Hz, 2 H), 8.14 (d, J = 9.2 Hz, 2 H), 6.54 (d, J = 6.4 Hz, 1 H), 5.13 (d, J = 6.0 Hz, 1 H), 1.89-1.79 (m, 2 H), 1.75-1.68 (m, 2 H), 1.62-1.46 (6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 148.1, 138.8, 137.5, 128.4, 123.5, 110.6, 52.7, 41.2, 25.9, 21.1; HRMS calcd for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: 273.1234, found 273.1234.



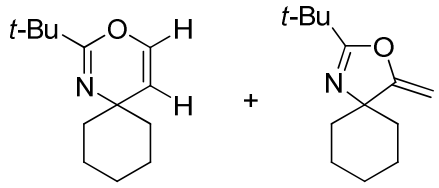
T

Oxazine T: (157.7 mg, 96%); IR (neat) δ 2927, 2854, 1689, 1450, 1284, 1219, 1057, 694 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.2 Hz, 2 H), 7.46-7.37 (m, 3 H), 6.54 (d, J = 6.4 Hz, 1 H), 5.14 (d, J = 6.0 Hz, 1 H), 1.85-1.79 (m, 2 H), 1.78-1.69 (m, 2 H), 1.60-1.44 (m, 6 H); HRMS calcd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1388, found: 228.1384.



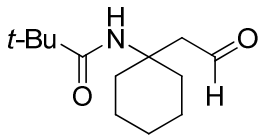
U

Amide U: (40.2 mg, 80 %); IR (neat) 2931, 2854, 1685, 1608, 1512, 1254, 1219, 1060, 1033, 841 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.2 Hz, 2 H), 6.90 (d, J = 7.2 Hz, 2 H), 6.54 (d, J = 6.0 Hz, 1 H), 5.13 (d, J = 6.4 Hz, 1 H), 3.84 (s, 3 H), 1.84 – 1.80 (m, 2 H), 1.72 – 1.66 (m, 2 H), 1.59 – 1.45 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 149.5, 137.7, 129.1, 125.6, 113.5, 110.5, 55.5, 51.9, 41.2, 26.0, 21.3; HRMS calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1494, found: 258.1489.



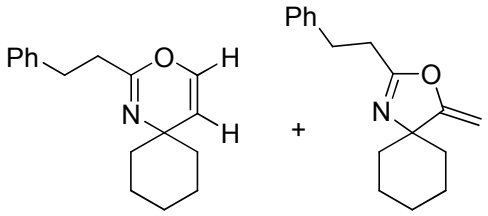
V **W**

Oxazine V and Exo-Product W: (from crude reaction mixture) ^{1}H (400 HMz, $CDCl_3$) δ 6.31 (d, J = 6.4 Hz, 1 H, endo), 4.93 (d, J = 6.0 Hz, 1 H, endo), 4.52 (d, J = 2.4 Hz, 0.14 H, exo), 4.08 (d, J = 2.8 Hz, 0.14 H, exo), 1.78 – 1.66 (m), 1.51 – 1.46 (m), 1.43 – 1.31 (m), 1.21 (s, 1.3 H), 1.11 (s, 9 H).



X

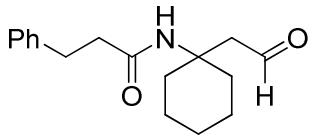
Aldehyde X: (41.8 mg, 77%); IR (neat) 3456, 3406, 2931, 2862, 1716, 1662, 1516, 1454, 1203 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 9.71 (t, J = 2.4 Hz, 1 H), 5.52 (s, 1 H), 2.91 (d, J = 2.4 Hz, 2 H), 2.05 – 2.00 (m, 2 H), 1.60 – 1.52 (m, 3 H), 1.45 – 1.38 (m, 5 H), 1.17 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 178.4, 53.8, 51.4, 39.5, 35.4, 27.8, 25.5, 21.6; HRMS calcd for $C_{13}H_{24}NO_2$ $[M+H]^+$: 226.1807, found: 226.1802.



Y **Z**

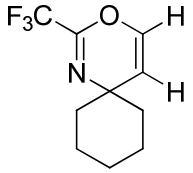
Oxazine Y and exo-product Z: (12.0 mg, 24%, isolated as 1:1 mixture) IR (neat) 2931, 2854, 1697, 1450, 1219, 1057, 968, 744 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 10 H), 6.37 (d, J = 6.4 Hz, 1 H), 5.13 (d, J = 6.0 Hz, 1 H), 4.63 (d, J = 2.4 Hz, 1 H), 4.17 (d, J = 2.8 Hz, 1 H), 3.03 (t, J = 7.2 Hz, 2 H), 2.96 (d, J = 7.6 Hz, 2 H), 2.71 (d, J = 8.8 Hz, 2 H), 2.53 (t, J = 8.4 Hz, 2 H), 1.79 – 1.35 (m, 20 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 162.5, 153.6, 141.2, 140.5, 137.3,

128.6, 128.5, 126.5, 126.2, 109.6, 82.2, 82.1, 71.5, 51.7, 41.1, 39.1, 36.3, 32.4, 32.2, 30.3, 29.9, 25.8, 25.6, 22.2, 21.3.



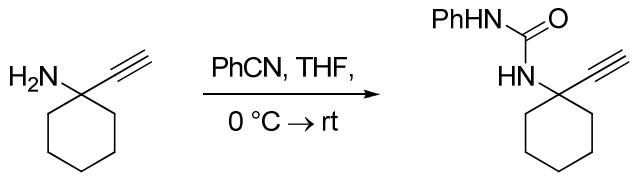
AA

Aldehyde AA: (30.1 mg, 56%); IR (neat) 3317, 2931, 2858, 1716, 1651, 1539, 1450 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 9.60 (t, J = 2.4 Hz, 1 H), 7.28 (m, 2 H), 7.22 (m, 3 H), 5.28 (s, 1 H), 2.95 (t, J = 7.6 Hz, 2 H), 2.88 (d, J = 2.4 Hz, 2 H), 2.49 (t, J = 7.6 Hz, 2 H), 2.04 – 2.02 (m, 2 H), 1.49 – 1.38 (m, 4 H), 1.29 – 1.24 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 172.1, 140.8, 128.7, 128.5, 126.5, 54.4, 51.2, 39.1, 35.3, 31.8, 25.4, 21.4; HRMS calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1807, found: 274.1802.



AB

Oxazine AB (product was extremely volatile and could not be well isolated): (0.5 mg, <1%); ^1H (400 MHz, $CDCl_3$) δ 6.42 (d, J = 6.0 Hz, 1 H), 5.15 (d, J = 6.0 Hz, 1 H), 1.75-1.66 (m, 4 H), 1.59-1.52 (m, 2 H), 1.51-1.40 (m, 4 H).

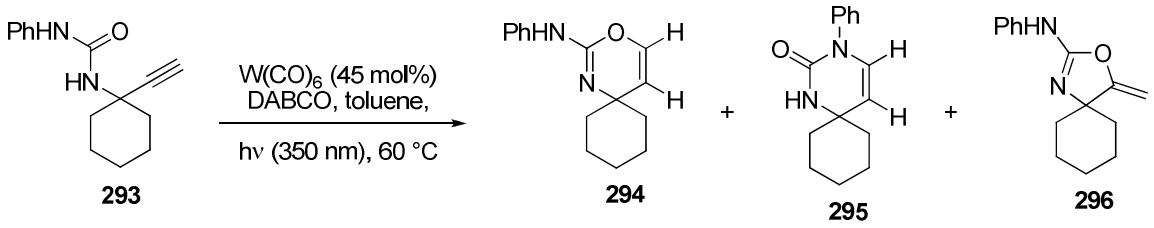


AC **293**

Urea 293: In a dry 25 mL round bottomed flask was added alkyne **AC** (0.33 mL, 2.93 mmol) in THF (10 mL) under argon, and the reaction mixture was cooled to

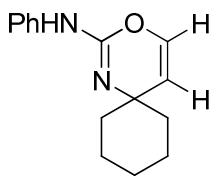
0 ℃ (ice bath). Phenylisocyanate (0.35 mL, 3.22 mmol) was added, and the reaction warmed slowly to rt over 2 h. The reaction was stirred at ambient temperature for an additional 23 h. The reaction mixture was diluted with Et_2O (50 mL) and washed with HCl (0.5 M, 25 mL), then $NaHCO_3$ saturated solution (25 mL). The organic layer was dried over Na_2SO_4, and solvent removed by reduced pressure. The crude reaction mixture was then chromatographed (8 : 2, hexanes : EtOAc) to provide urea **293** (541.2 mg, 91%).

Urea 293: m.p. = 129 ℃ – 130 ℃; IR (neat) 3532, 3305, 2935, 2858, 1655, 1550, 1241 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.31 (m, 2 H), 7.26 (m, 2 H), 7.11 (s, 1 H), 7.02 (m, 1 H), 4.87 (s, 1 H), 2.53 (s, 1 H), 2.16 – 2.09 (m, 2 H), 1.65 – 1.54 (m, 7 H), 1.28 – 1.20 (m, 1 H); ^{13}C NMR (100 MHz, 154.8, 138.7, 129.3, 123.8, 120.6, 86.0, 73.3, 51.5, 38.2, 25.3, 22.5; HRMS calcd for $C_{15}H_{19}N_2O$ $[M+H]^+$: 243.1492; found: 243.1493.



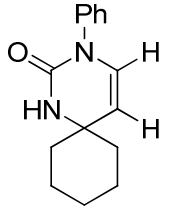
293 **294** **295** **296**

The same procedure was used as for the previous oxazine cycloisomerizations to provide oxazine **294** (7.8 mg, 16%), urea **295** (10.8 mg, 22 %), and exo-cyclic product **296** (18.6 mg, 37.%).



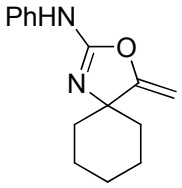
294

Oxazine 294: IR (neat) 3413, 2927, 2854, 1685, 1411, 1257 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$) δ 7.38 (m, 2 H), 7.32 – 7.23 (m, 3 H), 6.20 (d, J = 7.6 Hz, 1 H), 5.21 (s, 1 H), 5.00 (d, J = 8.0 Hz, 1 H), 1.77 – 1.71 (m, 2 H), 1.67 – 1.57 (m, 6 H), 1.48 – 1.43 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 140.9, 129.2, 127.5, 126.8, 126.4, 108.0, 55.7, 40.5, 25.2, 21.5.



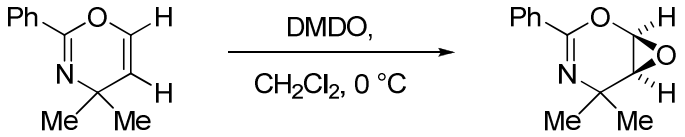
295

Urea 295: ^{1}H (400 MHz, $CDCl_3$) δ 7.35 (m, 2 H), 7.28 (m, 2 H), 7.05 (m, 1 H), 6.44 (d, J = 6.4 Hz, 1 H), 5.57 (d, J = 6.0 Hz, 1 H), 5.08 (s, 1 H), 2.16 (m, 2 H), 1.83 – 1.36 (m, 8 H).



296

Exo-product 296: ^{1}H (400 MHz, $CDCl_3$) δ 7.42 (m, 2 H), 7.31 (m, 2 H), 7.03 (m, 1 H), 4.61 (app s, 1 H), 4.18 (d, J = 2.8 Hz, 1 H), 1.78 – 1.68 (m, 6 H), 1.56 – 1.50 (m, 2 H), 1.34 – 1.27 (m, 2 H).



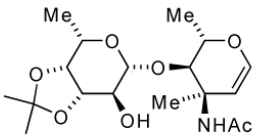
281 (±) **300**

Epoxide 300: In a dry 10 mL round bottomed flask was added **281** (13.8 mg, 0.074 mmol) in CH_2Cl_2 (1.5 mL) and the reaction mixture cooled to 0 °C (ice

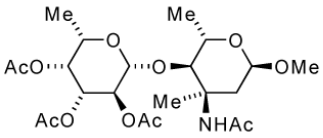
bath) under argon. Freshly prepared DMDO (5 mL in acetone, dried over $MgSO_4$) was added. After 3 h the reaction was still incomplete, additional DMDO was added (1.5 mL). After an additional 0.5 h, solvent was removed under reduced pressure to provide a 7.7 : 1 mixture of **300** : **281** which was not further purified.

Epoxide 300: ^1H (400 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2 H), 7.45-7.35 (m, 3 H), 5.27 (d, J = 2.8 Hz, 1 H), 3.12 (d, J = 2.8 Hz, 1 H), 1.43 (s, 3 H), 1.38 (s, 3 H).

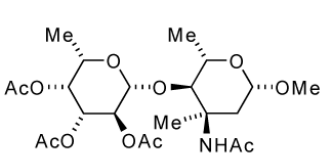
3.2. Pertinent COSY NMR spectra



182



135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O
OMe
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AcO
OAc
NHAc

184

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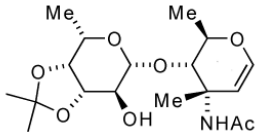
2.0
1.0
F1 (ppm)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O
O
O
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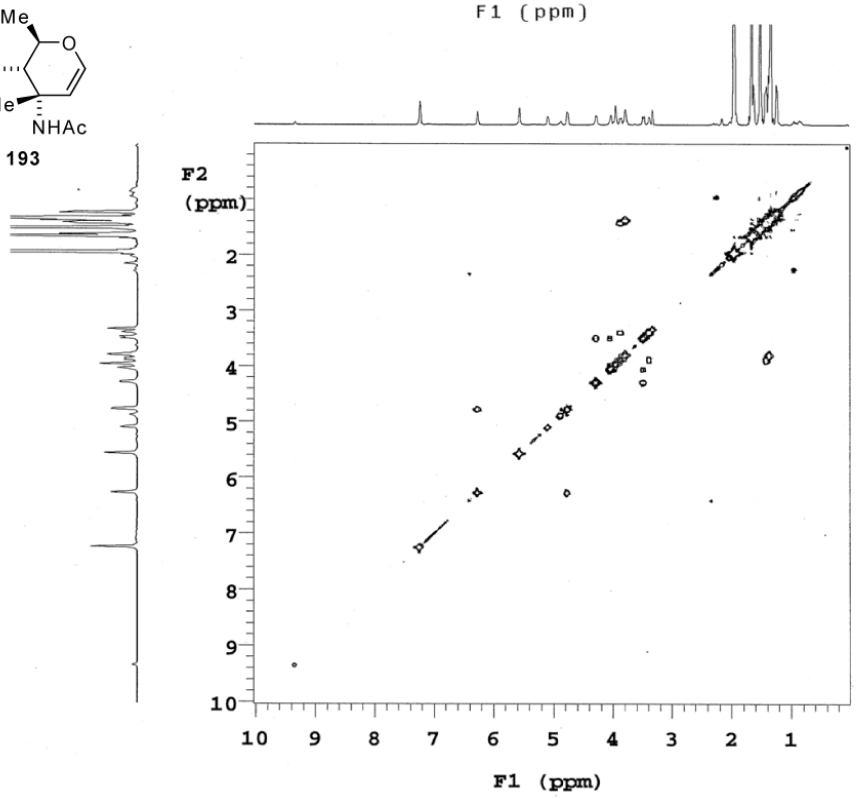
OH
NHAc

193


F2
(ppm)
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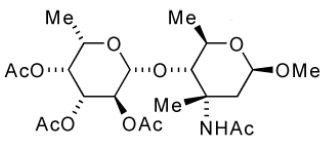
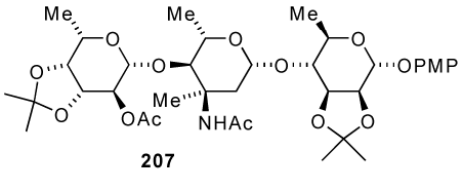
1
F1 (ppm)


Me
Me
AcO
O
OMe
Me
AcO
OAc
NHAc

194

A
B
C
D
E
F
G
H
J
K
a
R
S
F2
(ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
F1 (ppm)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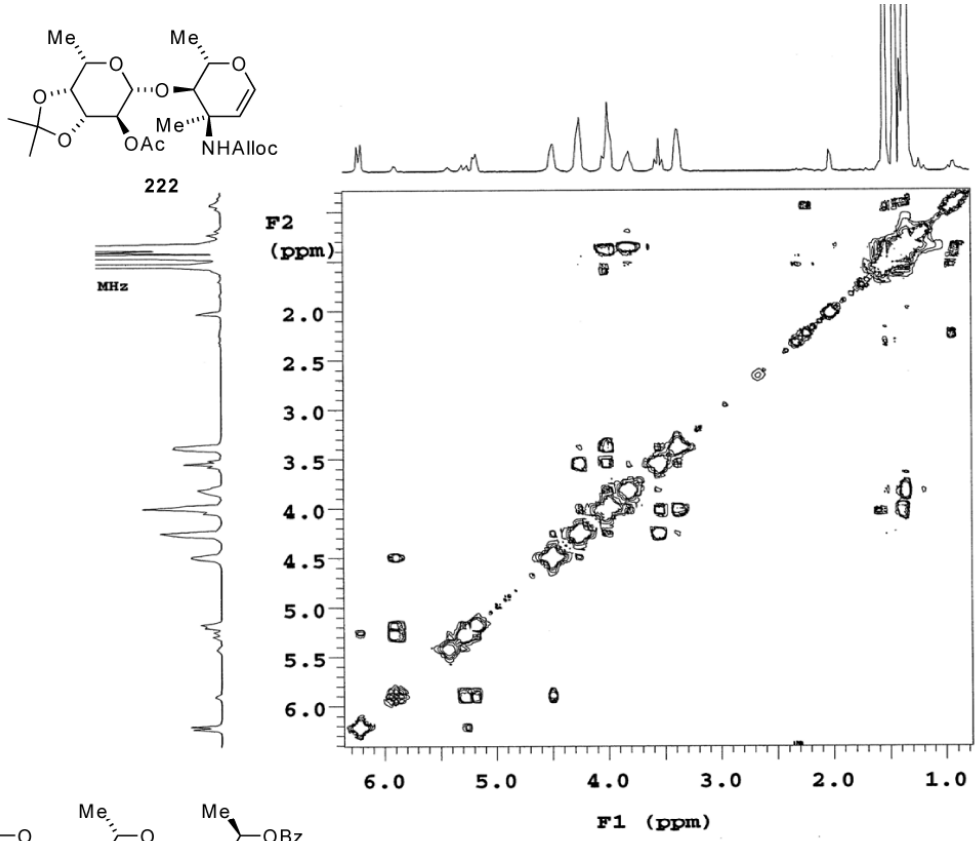
Me
O
O
O
O
O
OPMP
Me
OAc
NHAc
O
O

207

F2
(ppm)
2
3
4
5
6
7
7 6 5 4 3 2 1
F1 (ppm)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O
O
O
Me
OAc
NHAlloc
222
MHz
F2
(ppm)
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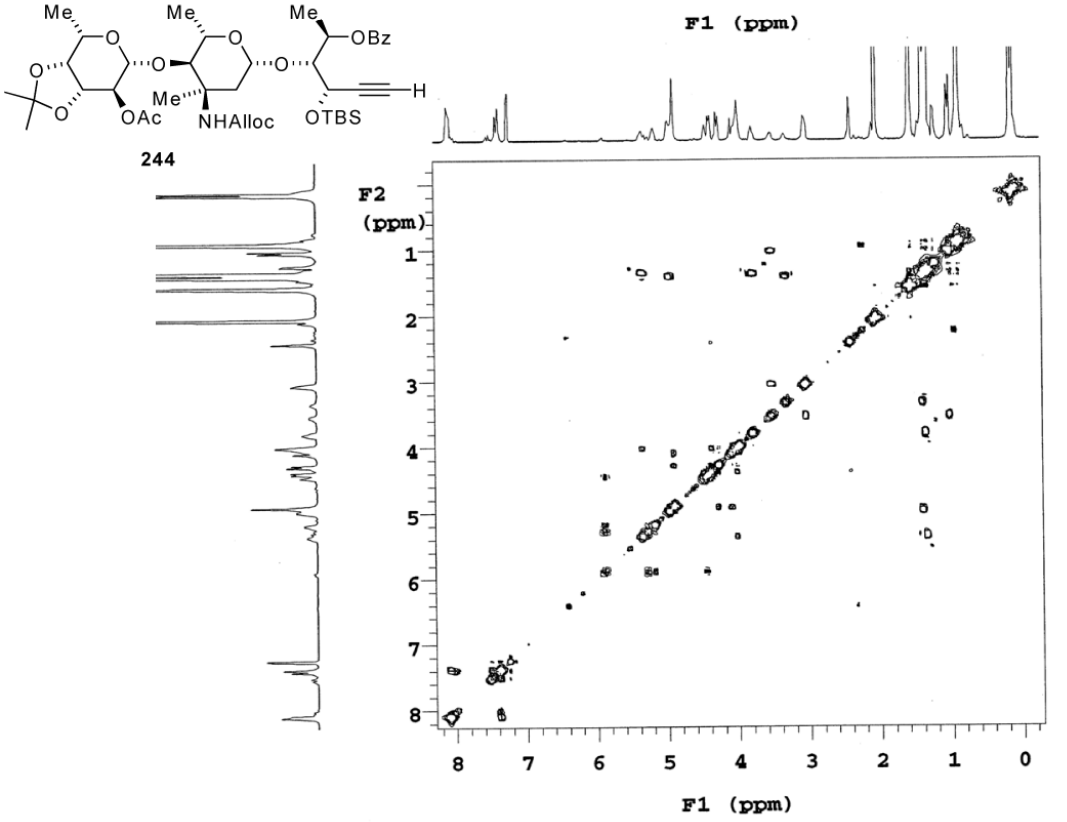
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.0
4.0
3.0
2.0
1.0
F1 (ppm)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Me
Me
OBz
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O
O
O
O
Me
H
OAc
NHAlloc
OTBS
244
F2
(ppm)
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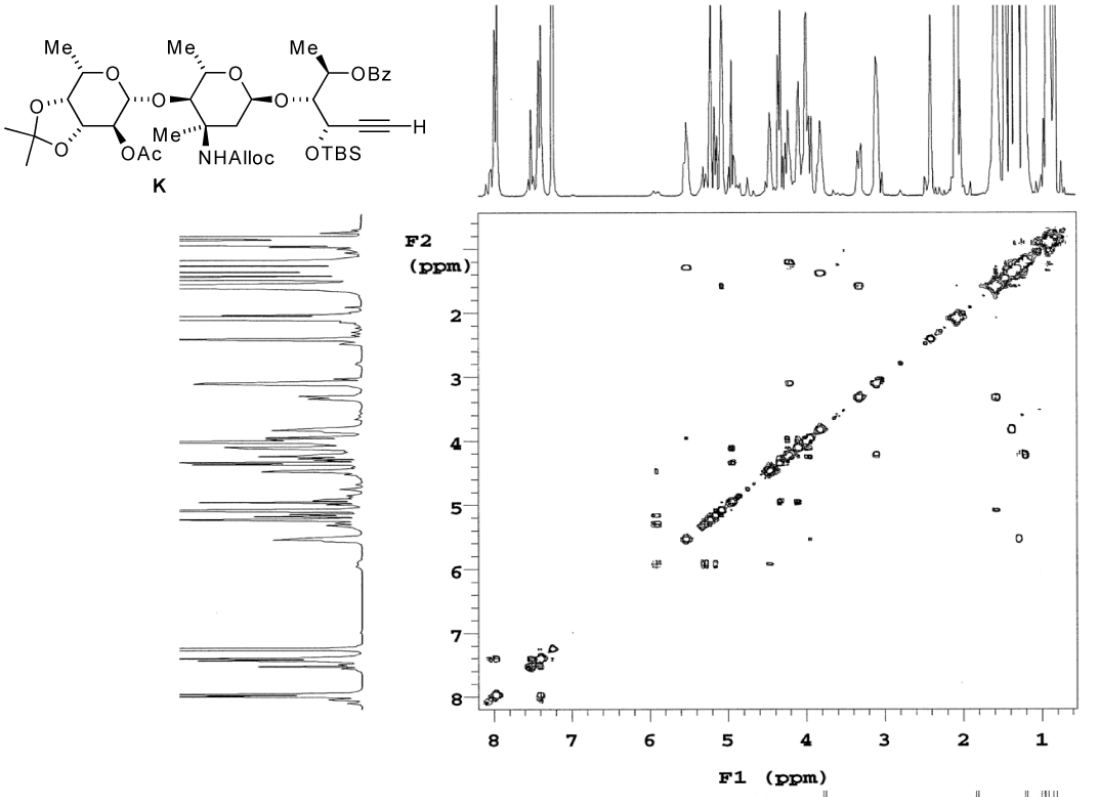
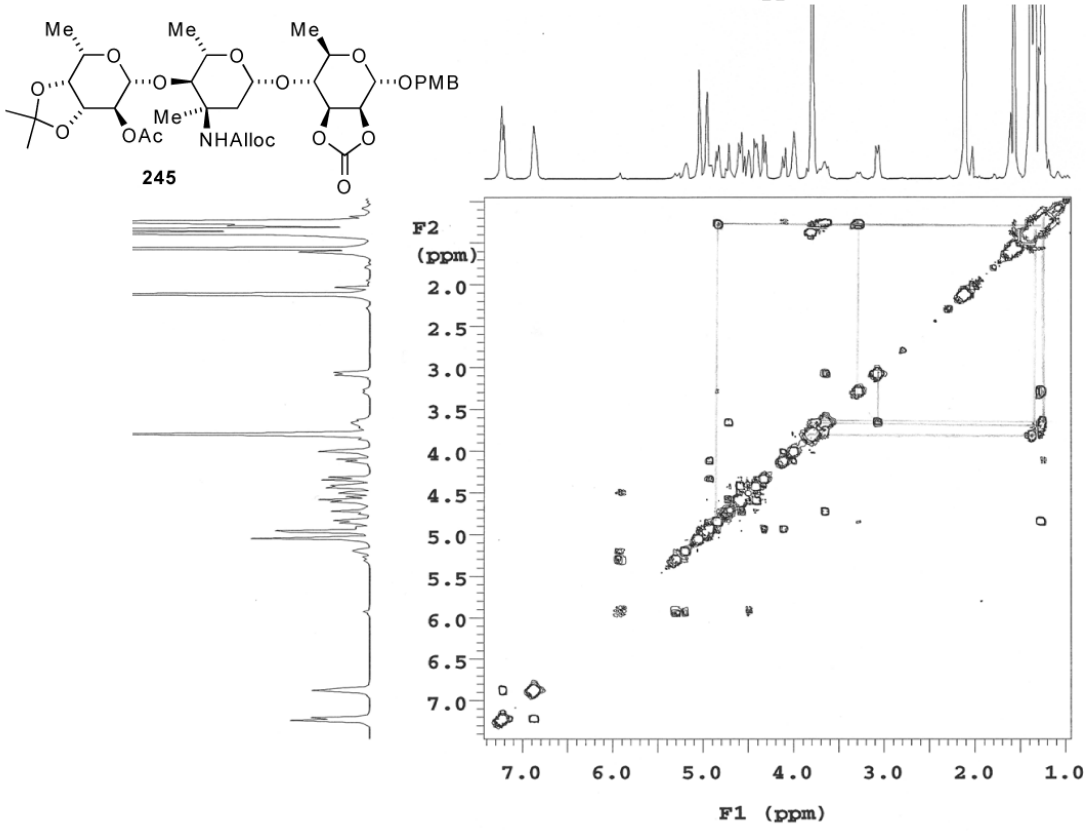
2
3
4
5
6
7
8
8
7
6
5
4
3
2
1
0
F1 (ppm)


Me
Me
Me
OBz
O
O
O
O
O
Me
H
OAc
NHAlloc
OTBS
K
F2
(ppm)
F1 (ppm)


Me
Me
Me
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O
O
O
O
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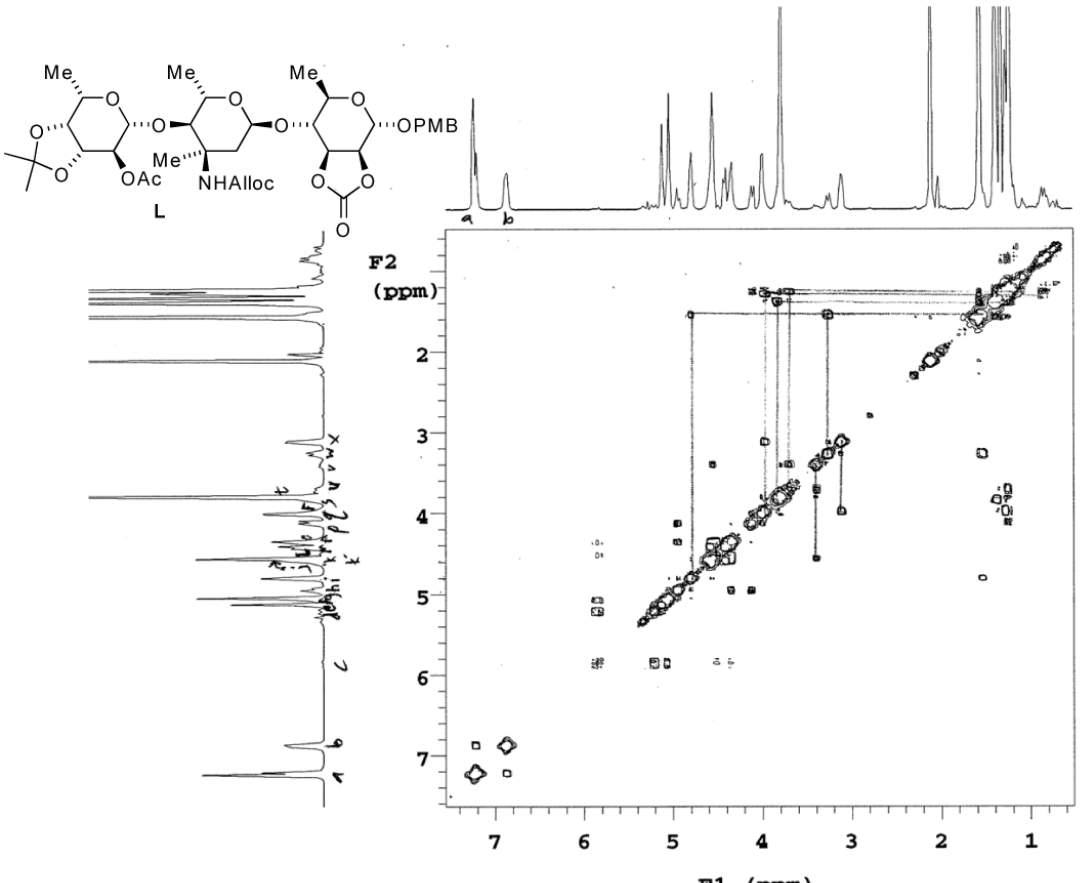
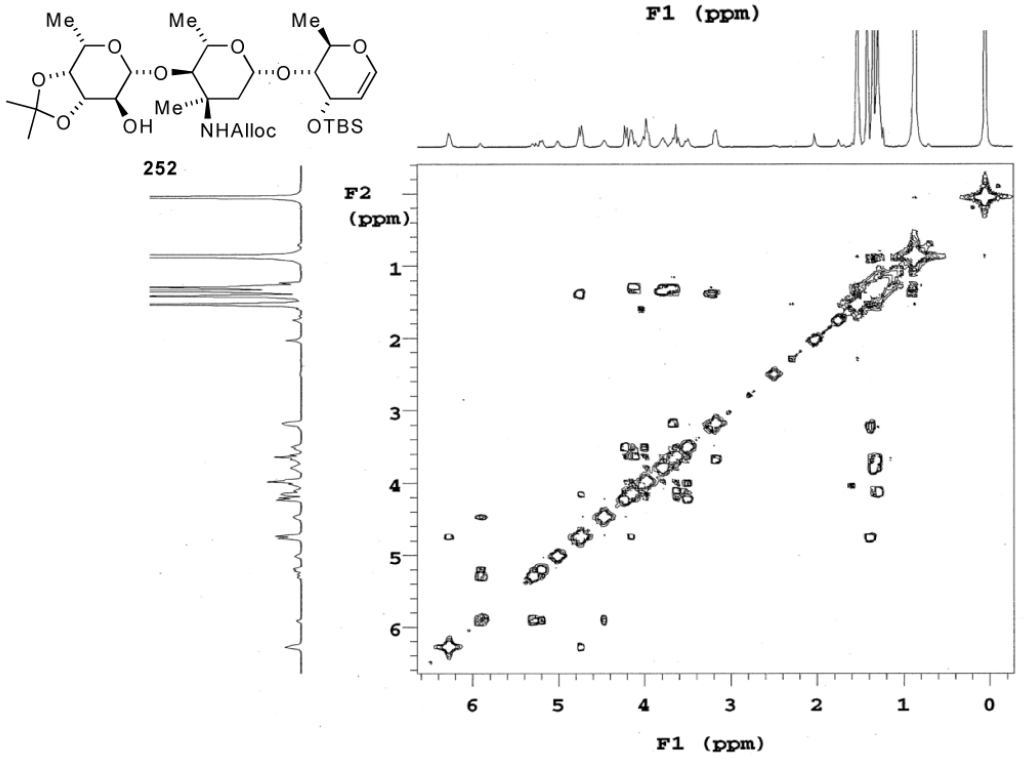
OPMB
Me
OAc
NHAlloc
O
O
O
245
F2
(ppm)
F1 (ppm)


Me
Me
Me
OPMB
OAc
Me
NHAlloc
L
a
b
F2
(ppm)
F1 (ppm)


Me
Me
Me
OH
Me
NHAlloc
OTBS
252
F2
(ppm)
F1 (ppm)

3.3. X-Ray database in the saccharomicin synthesis

The absolute stereochemistry of β-lactam-β-glycosideacetonide **165** was confirm by single crystal X-ray analysis carried out on crystals grown at ambient temperature in a mixture of chloroform and heptane; absolute structure parameter -0.2(3). The thermal ellipsoid diagram is shown below:

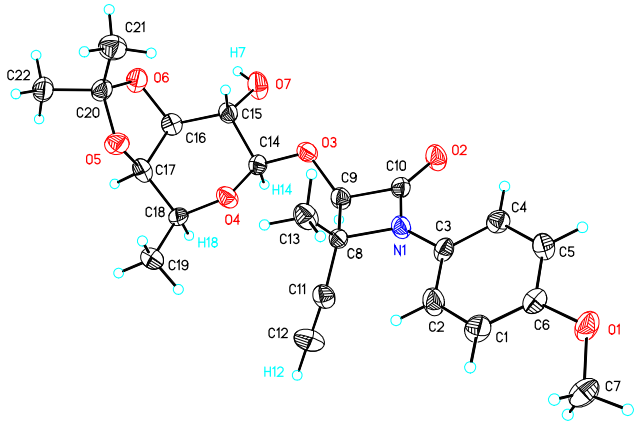


Table 3.1: Crystal data and structure refinement for compound **165**

Identification code	B20636B	
Empirical formula	C22 H27 N O7	
Formula weight	417.45	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.715(3) Å	□= 90°.
	b = 15.086(5) Å	□= 96.54(3)°.
	c = 9.295(3) Å	□ = 90°.
Volume	1074.9(6) Å^3	
Z	2	
Density (calculated)	1.290 Mg/m^3	
Absorption coefficient	0.799 mm^{-1}	
F(000)	444	
Crystal size	0.42 x 0.12 x 0.08 mm^3	

Theta range for data collection	4.79 to 65.77°.
Index ranges	-9<=h<=5, -17<=k<=14, -8<=l<=10
Reflections collected	3227
Independent reflections	2005 [R(int) = 0.0288]
Completeness to theta = 65.77°	77.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9388 and 0.7301
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2005 / 1 / 277
Goodness-of-fit on F^2	1.103
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0877
R indices (all data)	R1 = 0.0403, wR2 = 0.0926
Absolute structure parameter	-0.2(3)
Largest diff. peak and hole	0.150 and -0.215 e.$Å^{-3}$

Table 3.2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for **165**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6436(6)	-899(3)	7320(4)	35(1)
C(2)	5927(5)	-48(3)	7626(4)	36(1)
C(3)	4366(5)	105(2)	8177(4)	25(1)
C(4)	3266(5)	-615(3)	8371(4)	29(1)
C(5)	3786(5)	-1464(2)	8073(4)	31(1)
C(6)	5373(5)	-1612(2)	7545(4)	28(1)
C(7)	7589(5)	-2666(3)	7167(5)	40(1)
C(8)	4569(4)	1853(2)	8024(4)	25(1)
C(9)	3295(4)	2286(2)	9053(4)	27(1)
C(10)	2644(5)	1340(2)	9258(4)	26(1)
C(11)	6425(5)	2034(2)	8523(4)	30(1)
C(12)	7866(5)	2233(3)	8873(5)	45(1)
C(13)	4095(5)	1981(3)	6401(4)	33(1)
C(14)	2651(5)	3780(2)	8544(4)	26(1)
C(15)	1132(5)	4403(2)	8115(4)	27(1)

C(16)	1785(4)	5357(2)	7913(4)	28(1)
C(17)	3475(5)	5415(2)	7191(4)	30(1)
C(18)	4755(5)	4676(2)	7584(4)	27(1)
C(19)	6188(5)	4593(3)	6591(5)	39(1)
C(20)	1202(5)	5868(3)	5534(4)	32(1)
C(21)	-47(5)	5373(3)	4438(5)	43(1)
C(22)	1478(5)	6836(3)	5132(5)	40(1)
N(1)	3900(4)	980(2)	8515(3)	28(1)
O(1)	5790(3)	-2486(2)	7327(3)	36(1)
O(2)	1496(3)	1011(2)	9875(3)	38(1)
O(3)	2018(3)	2897(2)	8484(3)	28(1)
O(4)	3879(3)	3832(2)	7532(3)	30(1)
O(5)	2818(3)	5396(2)	5697(3)	33(1)
O(6)	579(3)	5852(2)	6942(3)	36(1)
O(7)	-27(4)	4356(2)	9191(3)	41(1)

Table 3.3: Bond lengths [Å] and angles [°] for **165**

C(1)-C(6)	1.382(5)	C(8)-C(11)	1.480(5)
C(1)-C(2)	1.381(5)	C(8)-N(1)	1.504(5)
C(1)-H(1)	0.9500	C(8)-C(13)	1.523(6)
C(2)-C(3)	1.381(4)	C(8)-C(9)	1.588(4)
C(2)-H(2)	0.9500	C(9)-O(3)	1.407(4)
C(3)-C(4)	1.402(5)	C(9)-C(10)	1.532(5)
C(3)-N(1)	1.412(5)	C(9)-H(9)	1.0000
C(4)-C(5)	1.380(5)	C(10)-O(2)	1.215(4)
C(4)-H(4)	0.9500	C(10)-N(1)	1.366(4)
C(5)-C(6)	1.388(5)	C(11)-C(12)	1.162(6)
C(5)-H(5)	0.9500	C(12)-H(12)	0.9500
C(6)-O(1)	1.379(4)	C(13)-H(13A)	0.9800
C(7)-O(1)	1.438(4)	C(13)-H(13B)	0.9800
C(7)-H(7A)	0.9800	C(13)-H(13C)	0.9800
C(7)-H(7B)	0.9800	C(14)-O(4)	1.411(4)
C(7)-H(7C)	0.9800	C(14)-O(3)	1.418(4)

C(14)-C(15)	1.520(5)	C(2)-C(3)-N(1)	119.6(3)
C(14)-H(14)	1.0000	C(4)-C(3)-N(1)	121.4(3)
C(15)-O(7)	1.417(4)	C(5)-C(4)-C(3)	119.9(3)
C(15)-C(16)	1.543(5)	C(5)-C(4)-H(4)	120.0
C(15)-H(15)	1.0000	C(3)-C(4)-H(4)	120.0
C(16)-O(6)	1.431(5)	C(4)-C(5)-C(6)	120.6(3)
C(16)-C(17)	1.535(4)	C(4)-C(5)-H(5)	119.7
C(16)-H(16)	1.0000	C(6)-C(5)-H(5)	119.7
C(17)-O(5)	1.424(5)	O(1)-C(6)-C(1)	124.7(3)
C(17)-C(18)	1.506(5)	O(1)-C(6)-C(5)	115.9(3)
C(17)-H(17)	1.0000	C(1)-C(6)-C(5)	119.4(3)
C(18)-O(4)	1.440(4)	O(1)-C(7)-H(7A)	109.5
C(18)-C(19)	1.523(5)	O(1)-C(7)-H(7B)	109.5
C(18)-H(18)	1.0000	H(7A)-C(7)-H(7B)	109.5
C(19)-H(19A)	0.9800	O(1)-C(7)-H(7C)	109.5
C(19)-H(19B)	0.9800	H(7A)-C(7)-H(7C)	109.5
C(19)-H(19C)	0.9800	H(7B)-C(7)-H(7C)	109.5
C(20)-O(5)	1.429(4)	C(11)-C(8)-N(1)	114.8(3)
C(20)-O(6)	1.444(4)	C(11)-C(8)-C(13)	113.7(3)
C(20)-C(21)	1.517(6)	N(1)-C(8)-C(13)	111.1(3)
C(20)-C(22)	1.528(6)	C(11)-C(8)-C(9)	112.2(3)
C(21)-H(21A)	0.9800	N(1)-C(8)-C(9)	85.5(2)
C(21)-H(21B)	0.9800	C(13)-C(8)-C(9)	116.7(3)
C(21)-H(21C)	0.9800	O(3)-C(9)-C(10)	115.5(3)
C(22)-H(22A)	0.9800	O(3)-C(9)-C(8)	119.9(3)
C(22)-H(22B)	0.9800	C(10)-C(9)-C(8)	85.7(3)
C(22)-H(22C)	0.9800	O(3)-C(9)-H(9)	111.1
O(7)-H(7)	0.8400	C(10)-C(9)-H(9)	111.1
		C(8)-C(9)-H(9)	111.1
C(6)-C(1)-C(2)	120.2(3)	O(2)-C(10)-N(1)	132.3(3)
C(6)-C(1)-H(1)	119.9	O(2)-C(10)-C(9)	134.9(3)
C(2)-C(1)-H(1)	119.9	N(1)-C(10)-C(9)	92.7(2)
C(3)-C(2)-C(1)	120.8(4)	C(12)-C(11)-C(8)	175.3(5)
C(3)-C(2)-H(2)	119.6	C(11)-C(12)-H(12)	180.0
C(1)-C(2)-H(2)	119.6	C(8)-C(13)-H(13A)	109.5
C(2)-C(3)-C(4)	119.0(3)	C(8)-C(13)-H(13B)	109.5

H(13A)-C(13)-H(13B)	109.5	C(18)-C(19)-H(19A)	109.5
C(8)-C(13)-H(13C)	109.5	C(18)-C(19)-H(19B)	109.5
H(13A)-C(13)-H(13C)	109.5	H(19A)-C(19)-H(19B)	109.5
H(13B)-C(13)-H(13C)	109.5	C(18)-C(19)-H(19C)	109.5
O(4)-C(14)-O(3)	106.3(3)	H(19A)-C(19)-H(19C)	109.5
O(4)-C(14)-C(15)	110.2(3)	H(19B)-C(19)-H(19C)	109.5
O(3)-C(14)-C(15)	108.6(3)	O(5)-C(20)-O(6)	105.8(3)
O(4)-C(14)-H(14)	110.5	O(5)-C(20)-C(21)	107.8(3)
O(3)-C(14)-H(14)	110.5	O(6)-C(20)-C(21)	110.4(3)
C(15)-C(14)-H(14)	110.5	O(5)-C(20)-C(22)	111.0(3)
O(7)-C(15)-C(14)	108.3(3)	O(6)-C(20)-C(22)	107.9(3)
O(7)-C(15)-C(16)	112.0(3)	C(21)-C(20)-C(22)	113.7(4)
C(14)-C(15)-C(16)	110.9(3)	C(20)-C(21)-H(21A)	109.5
O(7)-C(15)-H(15)	108.5	C(20)-C(21)-H(21B)	109.5
C(14)-C(15)-H(15)	108.5	H(21A)-C(21)-H(21B)	109.5
C(16)-C(15)-H(15)	108.5	C(20)-C(21)-H(21C)	109.5
O(6)-C(16)-C(17)	102.6(3)	H(21A)-C(21)-H(21C)	109.5
O(6)-C(16)-C(15)	111.5(3)	H(21B)-C(21)-H(21C)	109.5
C(17)-C(16)-C(15)	114.3(3)	C(20)-C(22)-H(22A)	109.5
O(6)-C(16)-H(16)	109.4	C(20)-C(22)-H(22B)	109.5
C(17)-C(16)-H(16)	109.4	H(22A)-C(22)-H(22B)	109.5
C(15)-C(16)-H(16)	109.4	C(20)-C(22)-H(22C)	109.5
O(5)-C(17)-C(18)	111.9(3)	H(22A)-C(22)-H(22C)	109.5
O(5)-C(17)-C(16)	101.5(3)	H(22B)-C(22)-H(22C)	109.5
C(18)-C(17)-C(16)	114.7(3)	C(10)-N(1)-C(3)	134.3(3)
O(5)-C(17)-H(17)	109.5	C(10)-N(1)-C(8)	95.3(3)
C(18)-C(17)-H(17)	109.5	C(3)-N(1)-C(8)	130.2(2)
C(16)-C(17)-H(17)	109.5	C(6)-O(1)-C(7)	116.1(3)
O(4)-C(18)-C(17)	110.7(3)	C(9)-O(3)-C(14)	112.1(3)
O(4)-C(18)-C(19)	106.1(3)	C(14)-O(4)-C(18)	112.1(3)
C(17)-C(18)-C(19)	114.5(3)	C(17)-O(5)-C(20)	107.6(3)
O(4)-C(18)-H(18)	108.4	C(16)-O(6)-C(20)	108.7(2)
C(17)-C(18)-H(18)	108.4	C(15)-O(7)-H(7)	109.5
C(19)-C(18)-H(18)	108.4		

Symmetry transformations used to generate equivalent atoms:

Table 3.4: Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **165**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	39(2)	33(2)	37(2)	0(2)	18(2)	8(2)
C(2)	39(2)	28(2)	44(2)	5(2)	19(2)	2(2)
C(3)	32(2)	20(2)	25(2)	2(1)	6(2)	5(2)
C(4)	28(2)	30(2)	28(2)	0(2)	8(2)	5(2)
C(5)	34(2)	27(2)	31(2)	1(1)	5(2)	-4(2)
C(6)	34(2)	27(2)	22(2)	1(1)	1(2)	6(2)
C(7)	44(2)	35(2)	42(2)	-4(2)	8(2)	14(2)
C(8)	22(2)	18(2)	35(2)	1(1)	7(2)	2(2)
C(9)	27(2)	25(2)	31(2)	1(1)	10(2)	1(2)
C(10)	25(2)	26(2)	26(2)	4(1)	5(2)	2(2)
C(11)	32(2)	30(2)	31(2)	1(1)	14(2)	2(2)
C(12)	30(2)	54(3)	55(3)	-7(2)	13(2)	-2(2)
C(13)	35(2)	30(2)	36(2)	-3(2)	10(2)	-4(2)
C(14)	26(2)	21(2)	29(2)	0(1)	4(2)	-1(2)
C(15)	26(2)	28(2)	30(2)	3(1)	9(2)	0(2)
C(16)	31(2)	26(2)	26(2)	-1(1)	5(2)	1(2)
C(17)	34(2)	25(2)	32(2)	-1(1)	11(2)	-6(2)
C(18)	22(2)	28(2)	31(2)	2(1)	-1(2)	-2(2)
C(19)	27(2)	40(2)	52(3)	8(2)	10(2)	-1(2)
C(20)	29(2)	32(2)	35(2)	6(2)	9(2)	7(2)
C(21)	36(2)	46(3)	48(3)	0(2)	8(2)	5(2)
C(22)	37(2)	39(2)	44(2)	13(2)	13(2)	6(2)
N(1)	28(2)	25(2)	34(2)	3(1)	12(2)	-1(1)
O(1)	44(2)	23(1)	44(2)	-1(1)	13(2)	9(1)
O(2)	38(2)	29(2)	50(2)	4(1)	24(2)	0(1)
O(3)	23(1)	23(1)	40(2)	0(1)	6(1)	-1(1)
O(4)	26(1)	25(1)	40(2)	-2(1)	12(1)	-1(1)
O(5)	28(1)	40(2)	32(2)	4(1)	9(1)	10(1)
O(6)	36(1)	34(2)	40(2)	9(1)	19(1)	12(1)
O(7)	46(2)	28(2)	53(2)	5(1)	29(2)	6(1)

Table 3.5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **165**

	x	y	z	U(eq)
H(1)	7521	-995	6953	42
H(2)	6660	437	7455	43
H(4)	2164	-518	8708	34
H(5)	3052	-1951	8231	37
H(7A)	7874	-2417	6248	60
H(7B)	7782	-3308	7172	60
H(7C)	8337	-2394	7970	60
H(9)	3959	2516	9964	33
H(12)	9044	2396	9159	55
H(13A)	4526	2557	6112	50
H(13B)	2824	1958	6171	50
H(13C)	4629	1509	5877	50
H(14)	3215	3922	9540	31
H(15)	503	4195	7176	33
H(16)	1955	5662	8873	33
H(17)	4054	5998	7429	36
H(18)	5315	4777	8595	33
H(19A)	6975	4108	6929	58
H(19B)	6847	5149	6604	58
H(19C)	5663	4470	5601	58
H(21A)	-64	4745	4703	65
H(21B)	338	5434	3474	65
H(21C)	-1222	5622	4430	65
H(22A)	378	7161	5130	59
H(22B)	1871	6865	4167	59
H(22C)	2363	7102	5842	59
H(7)	-468	4857	9297	61

Table 3.6: Torsion angles [°] for **165**

C(6)-C(1)-C(2)-C(3)	0.8(7)
C(1)-C(2)-C(3)-C(4)	-2.4(6)
C(1)-C(2)-C(3)-N(1)	178.4(4)
C(2)-C(3)-C(4)-C(5)	2.9(6)
N(1)-C(3)-C(4)-C(5)	-178.0(4)
C(3)-C(4)-C(5)-C(6)	-1.7(6)
C(2)-C(1)-C(6)-O(1)	-177.4(4)
C(2)-C(1)-C(6)-C(5)	0.4(6)
C(4)-C(5)-C(6)-O(1)	178.0(3)
C(4)-C(5)-C(6)-C(1)	0.1(6)
C(11)-C(8)-C(9)-O(3)	121.6(4)
N(1)-C(8)-C(9)-O(3)	-123.5(3)
C(13)-C(8)-C(9)-O(3)	-12.2(5)
C(11)-C(8)-C(9)-C(10)	-121.4(3)
N(1)-C(8)-C(9)-C(10)	-6.4(3)
C(13)-C(8)-C(9)-C(10)	104.9(3)
O(3)-C(9)-C(10)-O(2)	-53.9(6)
C(8)-C(9)-C(10)-O(2)	-175.0(5)
O(3)-C(9)-C(10)-N(1)	128.2(3)
C(8)-C(9)-C(10)-N(1)	7.0(3)
N(1)-C(8)-C(11)-C(12)	-174(5)
C(13)-C(8)-C(11)-C(12)	56(5)
C(9)-C(8)-C(11)-C(12)	-79(5)
O(4)-C(14)-C(15)-O(7)	-177.6(3)
O(3)-C(14)-C(15)-O(7)	66.3(4)
O(4)-C(14)-C(15)-C(16)	-54.4(4)
O(3)-C(14)-C(15)-C(16)	-170.5(3)
O(7)-C(15)-C(16)-O(6)	-84.5(4)
C(14)-C(15)-C(16)-O(6)	154.5(3)
O(7)-C(15)-C(16)-C(17)	159.7(3)
C(14)-C(15)-C(16)-C(17)	38.7(4)
O(6)-C(16)-C(17)-O(5)	-35.1(3)
C(15)-C(16)-C(17)-O(5)	85.7(4)
O(6)-C(16)-C(17)-C(18)	-155.9(3)

C(15)-C(16)-C(17)-C(18)	-35.1(5)
O(5)-C(17)-C(18)-O(4)	-70.1(3)
C(16)-C(17)-C(18)-O(4)	44.8(4)
O(5)-C(17)-C(18)-C(19)	49.8(4)
C(16)-C(17)-C(18)-C(19)	164.7(3)
O(2)-C(10)-N(1)-C(3)	-0.3(8)
C(9)-C(10)-N(1)-C(3)	177.7(4)
O(2)-C(10)-N(1)-C(8)	174.6(5)
C(9)-C(10)-N(1)-C(8)	-7.4(3)
C(2)-C(3)-N(1)-C(10)	-167.9(4)
C(4)-C(3)-N(1)-C(10)	12.9(7)
C(2)-C(3)-N(1)-C(8)	18.8(6)
C(4)-C(3)-N(1)-C(8)	-160.4(4)
C(11)-C(8)-N(1)-C(10)	119.6(3)
C(13)-C(8)-N(1)-C(10)	-109.7(3)
C(9)-C(8)-N(1)-C(10)	7.2(3)
C(11)-C(8)-N(1)-C(3)	-65.2(5)
C(13)-C(8)-N(1)-C(3)	65.5(5)
C(9)-C(8)-N(1)-C(3)	-177.6(4)
C(1)-C(6)-O(1)-C(7)	14.2(5)
C(5)-C(6)-O(1)-C(7)	-163.7(3)
C(10)-C(9)-O(3)-C(14)	170.5(3)
C(8)-C(9)-O(3)-C(14)	-89.2(4)
O(4)-C(14)-O(3)-C(9)	69.4(4)
C(15)-C(14)-O(3)-C(9)	-172.0(3)
O(3)-C(14)-O(4)-C(18)	-174.3(3)
C(15)-C(14)-O(4)-C(18)	68.2(4)
C(17)-C(18)-O(4)-C(14)	-62.5(4)
C(19)-C(18)-O(4)-C(14)	172.7(3)
C(18)-C(17)-O(5)-C(20)	158.3(3)
C(16)-C(17)-O(5)-C(20)	35.5(3)
O(6)-C(20)-O(5)-C(17)	-22.5(4)
C(21)-C(20)-O(5)-C(17)	-140.6(3)
C(22)-C(20)-O(5)-C(17)	94.3(4)
C(17)-C(16)-O(6)-C(20)	22.6(4)
C(15)-C(16)-O(6)-C(20)	-100.2(3)

O(5)-C(20)-O(6)-C(16)	-1.6(4)
C(21)-C(20)-O(6)-C(16)	114.8(3)
C(22)-C(20)-O(6)-C(16)	-120.4(3)

Symmetry transformations used to generate equivalent atoms:

Table 3.7: Hydrogen bonds for **165** [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(7)-H(7)...O(2)#1	0.84	2.10	2.915(4)	165.2

Symmetry transformations used to generate equivalent atoms:
#1 -x,y+1/2,-z+2

The absolute stereochemistry of acetonide **166** was confirm by single crystal X-ray analysis carried out on crystals grown at ambient temperature in a mixture of chloroform and heptane; absolute structure parameter 0.0(1). The thermal ellipsoid diagram for is shown below:

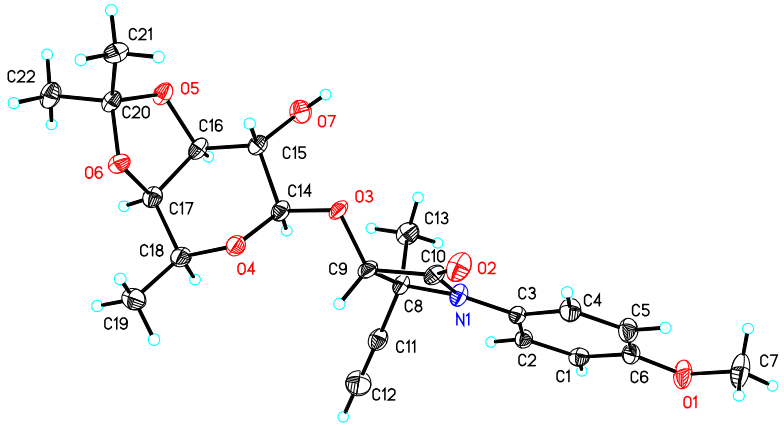


Table 3.8: Crystal data and structure refinement for **166**

Identification code	B20644As
Empirical formula	C22 H27 N O7
Formula weight	417.45

Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 13.2879(5) Å	□= 90°.
	b = 9.2997(4) Å	□= 100.194(2)°.
	c = 17.4110(7) Å	□ = 90°.
Volume	2117.57(15) $Å^3$	
Z	4	
Density (calculated)	1.309 Mg/m^3	
Absorption coefficient	0.812 mm^{-1}	
F(000)	888	
Crystal size	0.38 x 0.19 x 0.11 mm^3	
Theta range for data collection	2.58 to 66.34°.	
Index ranges	-15<=h<=15, -10<=k<=10, -18<=l<=20	
Reflections collected	12986	
Independent reflections	6137 [R(int) = 0.0279]	
Completeness to theta = 66.34°	92.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9160 and 0.7479	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6137 / 1 / 554	
Goodness-of-fit on F^2	1.094	
Final R indices [I>2sigma(I)]	R1 = 0.0481, wR2 = 0.1147	
R indices (all data)	R1 = 0.0483, wR2 = 0.1152	
Absolute structure parameter	0.0(1)	
Extinction coefficient	0.0168(8)	
Largest diff. peak and hole	0.435 and -0.314 e.$Å^{-3}$	

Table 3.9: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for **166**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8567(1)	5958(2)	7274(1)	19(1)

C(2)	7791(1)	5855(2)	6629(1)	18(1)
C(3)	7834(1)	6688(2)	5967(1)	17(1)
C(4)	8654(2)	7622(2)	5964(1)	22(1)
C(5)	9421(1)	7738(2)	6614(1)	24(1)
C(6)	9380(1)	6901(2)	7274(1)	21(1)
C(7)	10949(2)	7896(3)	7950(2)	41(1)
C(8)	6206(1)	5535(2)	5090(1)	18(1)
C(9)	5844(1)	6523(2)	4353(1)	18(1)
C(10)	6827(1)	7378(2)	4629(1)	18(1)
C(11)	5474(1)	5529(2)	5631(1)	21(1)
C(12)	4859(2)	5574(3)	6047(1)	33(1)
C(13)	6596(2)	4051(2)	4927(1)	26(1)
C(14)	4839(1)	5099(2)	3422(1)	19(1)
C(15)	4872(1)	4160(2)	2710(1)	18(1)
C(16)	3869(2)	3322(2)	2522(1)	20(1)
C(17)	2929(1)	4254(2)	2560(1)	20(1)
C(18)	3054(1)	5387(3)	3193(1)	22(1)
C(19)	2223(2)	6526(3)	3069(1)	31(1)
C(20)	2973(2)	3814(2)	1273(1)	19(1)
C(21)	3468(2)	4504(2)	648(1)	24(1)
C(22)	2003(2)	3001(2)	939(1)	26(1)
C(1B)	9732(2)	6187(2)	4328(1)	23(1)
C(2B)	8912(2)	6111(2)	3706(1)	22(1)
C(3B)	8726(1)	7231(2)	3173(1)	19(1)
C(4B)	9359(2)	8441(2)	3260(1)	22(1)
C(5B)	10163(1)	8517(2)	3886(1)	22(1)
C(6B)	10341(1)	7399(2)	4423(1)	20(1)
C(7B)	11481(2)	6461(3)	5519(2)	43(1)
C(8B)	7307(1)	8381(2)	2084(1)	18(1)
C(9B)	6577(1)	7152(2)	1674(1)	20(1)
C(10B)	7233(1)	6130(2)	2242(1)	20(1)
C(11B)	7912(2)	9065(3)	1560(1)	25(1)
C(12B)	8373(2)	9647(4)	1129(2)	48(1)
C(13B)	6836(2)	9459(2)	2574(1)	24(1)
C(14B)	4919(1)	8129(2)	1282(1)	17(1)
C(15B)	3915(1)	8283(2)	1588(1)	16(1)

C(16B)	3252(1)	9355(2)	1069(1)	18(1)
C(17B)	3192(1)	9043(2)	199(1)	20(1)
C(18B)	4174(2)	8490(2)	-38(1)	22(1)
C(19B)	3999(2)	7701(3)	-814(1)	31(1)
C(20B)	1634(1)	8512(2)	499(1)	23(1)
C(21B)	1084(2)	7236(3)	771(2)	33(1)
C(22B)	897(2)	9569(3)	26(2)	35(1)
N(1)	7054(1)	6600(2)	5306(1)	19(1)
N(1B)	7871(1)	7190(2)	2559(1)	20(1)
O(1)	10095(1)	6948(2)	7946(1)	32(1)
O(2)	7249(1)	8396(2)	4384(1)	27(1)
O(3)	5760(1)	5880(2)	3611(1)	19(1)
O(4)	4026(1)	6110(2)	3256(1)	20(1)
O(5)	3680(1)	2832(2)	1733(1)	22(1)
O(6)	2775(1)	4906(2)	1801(1)	19(1)
O(7)	5692(1)	3160(2)	2850(1)	25(1)
O(1B)	11144(1)	7625(2)	5027(1)	30(1)
O(2B)	7227(1)	4840(2)	2378(1)	26(1)
O(3B)	5551(1)	7175(2)	1782(1)	19(1)
O(4B)	4724(1)	7518(2)	528(1)	19(1)
O(5B)	2373(1)	8007(2)	59(1)	22(1)
O(6B)	2203(1)	9246(2)	1164(1)	24(1)
O(7B)	4075(1)	8822(2)	2363(1)	25(1)

Table 3.10: Bond lengths [Å] and angles [°] for **166**.

C(1)-C(2)	1.387(3)
C(1)-C(6)	1.392(3)
C(2)-C(3)	1.399(3)
C(3)-C(4)	1.394(3)
C(3)-N(1)	1.408(2)
C(4)-C(5)	1.387(3)
C(5)-C(6)	1.397(3)
C(6)-O(1)	1.372(2)
C(7)-O(1)	1.436(3)
C(8)-C(11)	1.469(3)
C(8)-N(1)	1.497(3)
C(8)-C(13)	1.519(3)
C(8)-C(9)	1.583(3)
C(9)-O(3)	1.410(2)
C(9)-C(10)	1.532(3)
C(10)-O(2)	1.216(3)
C(10)-N(1)	1.371(3)
C(11)-C(12)	1.186(3)
C(14)-O(3)	1.412(2)
C(14)-O(4)	1.423(2)
C(14)-C(15)	1.524(3)
C(15)-O(7)	1.421(2)
C(15)-C(16)	1.528(3)
C(16)-O(5)	1.428(2)
C(16)-C(17)	1.531(3)
C(17)-O(6)	1.434(2)
C(17)-C(18)	1.513(3)
C(18)-O(4)	1.443(2)
C(18)-C(19)	1.518(3)
C(20)-O(6)	1.426(2)
C(20)-O(5)	1.445(2)
C(20)-C(21)	1.510(3)
C(20)-C(22)	1.518(3)
C(1B)-C(6B)	1.380(3)
C(1B)-C(2B)	1.395(3)
C(2B)-C(3B)	1.388(3)

C(3B)-C(4B)	1.397(3)
C(3B)-N(1B)	1.415(2)
C(4B)-C(5B)	1.387(3)
C(5B)-C(6B)	1.390(3)
C(6B)-O(1B)	1.375(2)
C(7B)-O(1B)	1.404(3)
C(8B)-C(11B)	1.463(3)
C(8B)-N(1B)	1.502(3)
C(8B)-C(13B)	1.522(3)
C(8B)-C(9B)	1.585(3)
C(9B)-O(3B)	1.409(2)
C(9B)-C(10B)	1.528(3)
C(10B)-O(2B)	1.224(3)
C(10B)-N(1B)	1.353(3)
C(11B)-C(12B)	1.181(4)
C(14B)-O(4B)	1.411(2)
C(14B)-O(3B)	1.412(2)
C(14B)-C(15B)	1.529(2)
C(15B)-O(7B)	1.420(2)
C(15B)-C(16B)	1.518(3)
C(16B)-O(6B)	1.435(2)
C(16B)-C(17B)	1.530(3)
C(17B)-O(5B)	1.441(2)
C(17B)-C(18B)	1.526(3)
C(18B)-O(4B)	1.438(2)
C(18B)-C(19B)	1.518(3)
C(20B)-O(5B)	1.428(2)
C(20B)-O(6B)	1.437(2)
C(20B)-C(21B)	1.513(3)
C(20B)-C(22B)	1.523(3)

C(2)-C(1)-C(6)	120.63(17)
C(1)-C(2)-C(3)	119.72(17)
C(4)-C(3)-C(2)	119.63(18)
C(4)-C(3)-N(1)	119.76(17)
C(2)-C(3)-N(1)	120.60(17)

C(5)-C(4)-C(3)	120.48(18)
C(4)-C(5)-C(6)	119.90(18)
O(1)-C(6)-C(1)	116.16(18)
O(1)-C(6)-C(5)	124.20(19)
C(1)-C(6)-C(5)	119.63(18)
C(11)-C(8)-N(1)	113.34(16)
C(11)-C(8)-C(13)	113.77(18)
N(1)-C(8)-C(13)	112.45(15)
C(11)-C(8)-C(9)	112.41(16)
N(1)-C(8)-C(9)	85.80(14)
C(13)-C(8)-C(9)	116.13(16)
O(3)-C(9)-C(10)	115.61(14)
O(3)-C(9)-C(8)	117.41(16)
C(10)-C(9)-C(8)	85.82(14)
O(2)-C(10)-N(1)	131.95(18)
O(2)-C(10)-C(9)	135.62(18)
N(1)-C(10)-C(9)	92.36(15)
C(12)-C(11)-C(8)	177.0(2)
O(3)-C(14)-O(4)	107.65(15)
O(3)-C(14)-C(15)	109.63(15)
O(4)-C(14)-C(15)	110.04(15)
O(7)-C(15)-C(14)	111.52(16)
O(7)-C(15)-C(16)	108.44(15)
C(14)-C(15)-C(16)	108.45(15)
O(5)-C(16)-C(15)	111.50(15)
O(5)-C(16)-C(17)	102.40(15)
C(15)-C(16)-C(17)	112.87(16)
O(6)-C(17)-C(18)	110.89(17)
O(6)-C(17)-C(16)	100.72(14)
C(18)-C(17)-C(16)	116.11(16)
O(4)-C(18)-C(17)	111.09(15)
O(4)-C(18)-C(19)	107.74(17)
C(17)-C(18)-C(19)	113.48(17)
O(6)-C(20)-O(5)	105.58(15)
O(6)-C(20)-C(21)	108.45(16)
O(5)-C(20)-C(21)	110.16(16)

O(6)-C(20)-C(22)	111.07(16)
O(5)-C(20)-C(22)	108.77(16)
C(21)-C(20)-C(22)	112.58(17)
C(6B)-C(1B)-C(2B)	119.66(19)
C(3B)-C(2B)-C(1B)	120.22(19)
C(2B)-C(3B)-C(4B)	119.93(18)
C(2B)-C(3B)-N(1B)	120.62(18)
C(4B)-C(3B)-N(1B)	119.40(18)
C(5B)-C(4B)-C(3B)	119.47(18)
C(4B)-C(5B)-C(6B)	120.39(19)
O(1B)-C(6B)-C(1B)	125.09(19)
O(1B)-C(6B)-C(5B)	114.61(19)
C(1B)-C(6B)-C(5B)	120.30(19)
C(11B)-C(8B)-N(1B)	112.86(16)
C(11B)-C(8B)-C(13B)	112.91(18)
N(1B)-C(8B)-C(13B)	113.06(16)
C(11B)-C(8B)-C(9B)	113.16(16)
N(1B)-C(8B)-C(9B)	85.53(14)
C(13B)-C(8B)-C(9B)	116.58(15)
O(3B)-C(9B)-C(10B)	112.17(15)
O(3B)-C(9B)-C(8B)	117.28(16)
C(10B)-C(9B)-C(8B)	85.61(14)
O(2B)-C(10B)-N(1B)	131.32(18)
O(2B)-C(10B)-C(9B)	135.46(18)
N(1B)-C(10B)-C(9B)	93.22(16)
C(12B)-C(11B)-C(8B)	177.8(3)
O(4B)-C(14B)-O(3B)	108.14(15)
O(4B)-C(14B)-C(15B)	109.53(14)
O(3B)-C(14B)-C(15B)	107.71(15)
O(7B)-C(15B)-C(16B)	107.93(15)
O(7B)-C(15B)-C(14B)	111.78(15)
C(16B)-C(15B)-C(14B)	107.70(15)
O(6B)-C(16B)-C(15B)	110.99(15)
O(6B)-C(16B)-C(17B)	102.65(14)
C(15B)-C(16B)-C(17B)	112.83(16)
O(5B)-C(17B)-C(18B)	112.65(17)

O(5B)-C(17B)-C(16B)	101.55(14)
C(18B)-C(17B)-C(16B)	115.76(16)
O(4B)-C(18B)-C(19B)	106.56(17)
O(4B)-C(18B)-C(17B)	112.44(15)
C(19B)-C(18B)-C(17B)	113.56(16)
O(5B)-C(20B)-O(6B)	105.98(14)
O(5B)-C(20B)-C(21B)	109.05(17)
O(6B)-C(20B)-C(21B)	109.59(18)
O(5B)-C(20B)-C(22B)	111.05(18)
O(6B)-C(20B)-C(22B)	108.97(17)
C(21B)-C(20B)-C(22B)	112.02(17)
C(10)-N(1)-C(3)	133.61(17)
C(10)-N(1)-C(8)	95.28(15)
C(3)-N(1)-C(8)	131.03(16)
C(10B)-N(1B)-C(3B)	133.57(18)
C(10B)-N(1B)-C(8B)	95.54(14)
C(3B)-N(1B)-C(8B)	130.69(16)
C(6)-O(1)-C(7)	116.86(17)
C(9)-O(3)-C(14)	110.88(13)
C(14)-O(4)-C(18)	110.14(15)
C(16)-O(5)-C(20)	108.59(14)
C(20)-O(6)-C(17)	106.28(14)
C(6B)-O(1B)-C(7B)	118.01(18)
C(9B)-O(3B)-C(14B)	114.26(14)
C(14B)-O(4B)-C(18B)	111.77(15)
C(20B)-O(5B)-C(17B)	105.02(15)
C(16B)-O(6B)-C(20B)	108.88(14)

Symmetry transformations used to generate equivalent atoms:

Table 3.11: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **166**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	22(1)	20(1)	15(1)	2(1)	3(1)	3(1)

C(2)	18(1)	19(1)	16(1)	0(1)	3(1)	-2(1)
C(3)	15(1)	20(1)	15(1)	-2(1)	1(1)	2(1)
C(4)	22(1)	26(1)	18(1)	4(1)	4(1)	-4(1)
C(5)	20(1)	29(1)	21(1)	2(1)	3(1)	-6(1)
C(6)	17(1)	28(1)	17(1)	-2(1)	-1(1)	2(1)
C(7)	30(1)	51(2)	36(1)	2(1)	-11(1)	-13(1)
C(8)	18(1)	19(1)	14(1)	-1(1)	-1(1)	-3(1)
C(9)	21(1)	22(1)	10(1)	-2(1)	2(1)	-2(1)
C(10)	23(1)	19(1)	11(1)	1(1)	1(1)	-1(1)
C(11)	23(1)	24(1)	16(1)	2(1)	1(1)	-4(1)
C(12)	33(1)	41(1)	26(1)	4(1)	10(1)	-5(1)
C(13)	31(1)	23(1)	24(1)	0(1)	1(1)	3(1)
C(14)	20(1)	22(1)	13(1)	1(1)	1(1)	-4(1)
C(15)	21(1)	19(1)	14(1)	1(1)	1(1)	0(1)
C(16)	24(1)	19(1)	14(1)	1(1)	-1(1)	-5(1)
C(17)	21(1)	23(1)	16(1)	3(1)	3(1)	-3(1)
C(18)	19(1)	33(1)	16(1)	-3(1)	7(1)	-6(1)
C(19)	23(1)	36(1)	35(1)	-12(1)	7(1)	1(1)
C(20)	23(1)	17(1)	16(1)	-2(1)	-1(1)	-1(1)
C(21)	30(1)	24(1)	18(1)	-2(1)	6(1)	-2(1)
C(22)	28(1)	23(1)	26(1)	-2(1)	-3(1)	-5(1)
C(1B)	25(1)	22(1)	22(1)	5(1)	2(1)	1(1)
C(2B)	19(1)	19(1)	26(1)	0(1)	2(1)	-3(1)
C(3B)	15(1)	23(1)	17(1)	-3(1)	1(1)	1(1)
C(4B)	22(1)	23(1)	20(1)	4(1)	1(1)	-3(1)
C(5B)	19(1)	24(1)	22(1)	1(1)	-1(1)	-4(1)
C(6B)	15(1)	26(1)	18(1)	-3(1)	-1(1)	1(1)
C(7B)	38(1)	39(2)	43(2)	13(1)	-20(1)	-2(1)
C(8B)	17(1)	23(1)	13(1)	2(1)	-1(1)	-3(1)
C(9B)	16(1)	25(1)	18(1)	-2(1)	3(1)	-2(1)
C(10B)	14(1)	24(1)	21(1)	-4(1)	2(1)	1(1)
C(11B)	22(1)	32(1)	19(1)	1(1)	0(1)	-6(1)
C(12B)	43(1)	72(2)	28(1)	6(1)	8(1)	-28(1)
C(13B)	26(1)	24(1)	20(1)	-3(1)	1(1)	1(1)
C(14B)	16(1)	19(1)	16(1)	0(1)	0(1)	-2(1)
C(15B)	16(1)	18(1)	14(1)	-2(1)	2(1)	-1(1)

C(16B)	16(1)	18(1)	20(1)	-3(1)	0(1)	-1(1)
C(17B)	20(1)	19(1)	18(1)	3(1)	-2(1)	-1(1)
C(18B)	22(1)	27(1)	17(1)	7(1)	4(1)	-1(1)
C(19B)	31(1)	46(1)	17(1)	2(1)	4(1)	3(1)
C(20B)	17(1)	24(1)	25(1)	-6(1)	-1(1)	2(1)
C(21B)	23(1)	31(1)	45(1)	-2(1)	7(1)	-1(1)
C(22B)	23(1)	34(1)	42(1)	-1(1)	-7(1)	9(1)
N(1)	20(1)	21(1)	15(1)	2(1)	0(1)	-5(1)
N(1B)	16(1)	19(1)	22(1)	2(1)	-2(1)	-1(1)
O(1)	23(1)	45(1)	22(1)	4(1)	-7(1)	-5(1)
O(2)	33(1)	27(1)	19(1)	7(1)	0(1)	-8(1)
O(3)	21(1)	26(1)	10(1)	-4(1)	1(1)	-7(1)
O(4)	19(1)	23(1)	17(1)	-2(1)	2(1)	-3(1)
O(5)	27(1)	15(1)	20(1)	-4(1)	-5(1)	5(1)
O(6)	25(1)	16(1)	16(1)	-1(1)	3(1)	2(1)
O(7)	24(1)	24(1)	26(1)	2(1)	3(1)	2(1)
O(1B)	28(1)	30(1)	26(1)	6(1)	-13(1)	-5(1)
O(2B)	20(1)	20(1)	38(1)	-3(1)	1(1)	0(1)
O(3B)	12(1)	25(1)	19(1)	6(1)	0(1)	1(1)
O(4B)	18(1)	24(1)	14(1)	2(1)	1(1)	2(1)
O(5B)	17(1)	25(1)	21(1)	-6(1)	-1(1)	-1(1)
O(6B)	15(1)	29(1)	26(1)	-8(1)	1(1)	1(1)
O(7B)	31(1)	28(1)	15(1)	-4(1)	2(1)	2(1)

Table 3.12: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{3}) for **166**.

	x	y	z	U(eq)
H(1)	8544	5378	7720	23
H(2)	7231	5222	6637	21
H(4)	8687	8183	5513	27

H(5)	9973	8385	6610	28
H(7A)	11319	7618	7534	62
H(7B)	11409	7832	8456	62
H(7C)	10702	8886	7864	62
H(9)	5221	7091	4404	21
H(12)	4366	5611	6381	40
H(13A)	7020	3671	5401	39
H(13B)	7005	4116	4512	39
H(13C)	6014	3406	4762	39
H(14)	4741	4484	3874	23
H(15)	4947	4783	2255	22
H(16)	3886	2485	2885	23
H(17)	2333	3624	2606	24
H(18)	3033	4897	3701	27
H(19A)	2312	7175	3519	47
H(19B)	1551	6062	3011	47
H(19C)	2268	7077	2596	47
H(21A)	3000	5215	363	35
H(21B)	3621	3764	284	35
H(21C)	4103	4979	890	35
H(22A)	1720	2557	1365	40
H(22B)	2161	2252	583	40
H(22C)	1501	3670	654	40
H(1B)	9870	5410	4685	28
H(2B)	8481	5289	3647	26
H(4B)	9240	9205	2893	27
H(5B)	10595	9338	3949	26
H(7B1)	10919	6123	5770	64
H(7B2)	12054	6768	5920	64
H(7B3)	11704	5678	5211	64
H(9B)	6647	6987	1118	24
H(12B)	8744	10115	782	57
H(13D)	7375	9895	2960	36
H(13E)	6346	8966	2842	36
H(13F)	6482	10211	2235	36
H(14B)	5259	9086	1271	21

H(15B)	3560	7332	1567	19
H(16B)	3509	10354	1191	22
H(17B)	2971	9936	-103	24
H(18B)	4625	9336	-83	26
H(19D)	4660	7453	-954	47
H(19E)	3616	8321	-1218	47
H(19F)	3608	6821	-769	47
H(21D)	673	6762	318	49
H(21E)	636	7565	1126	49
H(21F)	1586	6555	1043	49
H(22D)	1285	10286	-214	52
H(22E)	495	10052	370	52
H(22F)	438	9049	-383	52
H(7)	6222	3541	2740	37
H(7B4)	4184	8134	2679	37

Table 3.13: Torsion angles [°] for **166**.

C(6)-C(1)-C(2)-C(3)	1.2(3)
C(1)-C(2)-C(3)-C(4)	-0.5(3)
C(1)-C(2)-C(3)-N(1)	180.00(17)
C(2)-C(3)-C(4)-C(5)	-0.5(3)
N(1)-C(3)-C(4)-C(5)	179.02(18)
C(3)-C(4)-C(5)-C(6)	0.8(3)
C(2)-C(1)-C(6)-O(1)	178.46(17)
C(2)-C(1)-C(6)-C(5)	-0.9(3)
C(4)-C(5)-C(6)-O(1)	-179.4(2)
C(4)-C(5)-C(6)-C(1)	-0.1(3)
C(11)-C(8)-C(9)-O(3)	-123.74(18)
N(1)-C(8)-C(9)-O(3)	122.72(16)
C(13)-C(8)-C(9)-O(3)	9.7(2)
C(11)-C(8)-C(9)-C(10)	119.50(17)
N(1)-C(8)-C(9)-C(10)	5.95(13)
C(13)-C(8)-C(9)-C(10)	-107.04(17)
O(3)-C(9)-C(10)-O(2)	58.1(3)

C(8)-C(9)-C(10)-O(2)	176.6(2)
O(3)-C(9)-C(10)-N(1)	-124.97(17)
C(8)-C(9)-C(10)-N(1)	-6.49(14)
N(1)-C(8)-C(11)-C(12)	86(5)
C(13)-C(8)-C(11)-C(12)	-144(5)
C(9)-C(8)-C(11)-C(12)	-9(5)
O(3)-C(14)-C(15)-O(7)	60.3(2)
O(4)-C(14)-C(15)-O(7)	178.51(14)
O(3)-C(14)-C(15)-C(16)	179.64(15)
O(4)-C(14)-C(15)-C(16)	-62.15(19)
O(7)-C(15)-C(16)-O(5)	-79.57(18)
C(14)-C(15)-C(16)-O(5)	159.18(16)
O(7)-C(15)-C(16)-C(17)	165.81(15)
C(14)-C(15)-C(16)-C(17)	44.6(2)
O(5)-C(16)-C(17)-O(6)	-37.24(17)
C(15)-C(16)-C(17)-O(6)	82.76(18)
O(5)-C(16)-C(17)-C(18)	-157.03(16)
C(15)-C(16)-C(17)-C(18)	-37.0(2)
O(6)-C(17)-C(18)-O(4)	-71.6(2)
C(16)-C(17)-C(18)-O(4)	42.6(2)
O(6)-C(17)-C(18)-C(19)	50.0(2)
C(16)-C(17)-C(18)-C(19)	164.13(17)
C(6B)-C(1B)-C(2B)-C(3B)	1.6(3)
C(1B)-C(2B)-C(3B)-C(4B)	-0.1(3)
C(1B)-C(2B)-C(3B)-N(1B)	-177.31(17)
C(2B)-C(3B)-C(4B)-C(5B)	-0.8(3)
N(1B)-C(3B)-C(4B)-C(5B)	176.44(18)
C(3B)-C(4B)-C(5B)-C(6B)	0.2(3)
C(2B)-C(1B)-C(6B)-O(1B)	177.39(19)
C(2B)-C(1B)-C(6B)-C(5B)	-2.3(3)
C(4B)-C(5B)-C(6B)-O(1B)	-178.33(18)
C(4B)-C(5B)-C(6B)-C(1B)	1.4(3)
C(11B)-C(8B)-C(9B)-O(3B)	-132.10(19)
N(1B)-C(8B)-C(9B)-O(3B)	114.92(17)
C(13B)-C(8B)-C(9B)-O(3B)	1.3(2)
C(11B)-C(8B)-C(9B)-C(10B)	115.18(18)

N(1B)-C(8B)-C(9B)-C(10B)	2.20(12)
C(13B)-C(8B)-C(9B)-C(10B)	-111.39(17)
O(3B)-C(9B)-C(10B)-O(2B)	60.5(3)
C(8B)-C(9B)-C(10B)-O(2B)	178.3(2)
O(3B)-C(9B)-C(10B)-N(1B)	-120.16(16)
C(8B)-C(9B)-C(10B)-N(1B)	-2.44(14)
N(1B)-C(8B)-C(11B)-C(12B)	179(100)
C(13B)-C(8B)-C(11B)-C(12B)	-51(7)
C(9B)-C(8B)-C(11B)-C(12B)	84(7)
O(4B)-C(14B)-C(15B)-O(7B)	176.80(15)
O(3B)-C(14B)-C(15B)-O(7B)	59.4(2)
O(4B)-C(14B)-C(15B)-C(16B)	-64.80(19)
O(3B)-C(14B)-C(15B)-C(16B)	177.81(14)
O(7B)-C(15B)-C(16B)-O(6B)	-76.38(18)
C(14B)-C(15B)-C(16B)-O(6B)	162.77(15)
O(7B)-C(15B)-C(16B)-C(17B)	169.04(15)
C(14B)-C(15B)-C(16B)-C(17B)	48.2(2)
O(6B)-C(16B)-C(17B)-O(5B)	-34.22(18)
C(15B)-C(16B)-C(17B)-O(5B)	85.30(17)
O(6B)-C(16B)-C(17B)-C(18B)	-156.57(16)
C(15B)-C(16B)-C(17B)-C(18B)	-37.0(2)
O(5B)-C(17B)-C(18B)-O(4B)	-78.2(2)
C(16B)-C(17B)-C(18B)-O(4B)	38.0(2)
O(5B)-C(17B)-C(18B)-C(19B)	42.9(2)
C(16B)-C(17B)-C(18B)-C(19B)	159.11(18)
O(2)-C(10)-N(1)-C(3)	0.9(4)
C(9)-C(10)-N(1)-C(3)	-176.2(2)
O(2)-C(10)-N(1)-C(8)	-176.0(2)
C(9)-C(10)-N(1)-C(8)	6.87(15)
C(4)-C(3)-N(1)-C(10)	-8.5(3)
C(2)-C(3)-N(1)-C(10)	170.98(19)
C(4)-C(3)-N(1)-C(8)	167.43(19)
C(2)-C(3)-N(1)-C(8)	-13.1(3)
C(11)-C(8)-N(1)-C(10)	-119.29(18)
C(13)-C(8)-N(1)-C(10)	109.92(17)
C(9)-C(8)-N(1)-C(10)	-6.66(14)

C(11)-C(8)-N(1)-C(3)	63.7(3)
C(13)-C(8)-N(1)-C(3)	-67.1(2)
C(9)-C(8)-N(1)-C(3)	176.28(19)
O(2B)-C(10B)-N(1B)-C(3B)	-3.0(4)
C(9B)-C(10B)-N(1B)-C(3B)	177.61(18)
O(2B)-C(10B)-N(1B)-C(8B)	-178.1(2)
C(9B)-C(10B)-N(1B)-C(8B)	2.58(15)
C(2B)-C(3B)-N(1B)-C(10B)	-15.9(3)
C(4B)-C(3B)-N(1B)-C(10B)	166.9(2)
C(2B)-C(3B)-N(1B)-C(8B)	157.53(19)
C(4B)-C(3B)-N(1B)-C(8B)	-19.7(3)
C(11B)-C(8B)-N(1B)-C(10B)	-115.76(17)
C(13B)-C(8B)-N(1B)-C(10B)	114.55(17)
C(9B)-C(8B)-N(1B)-C(10B)	-2.49(14)
C(11B)-C(8B)-N(1B)-C(3B)	69.0(2)
C(13B)-C(8B)-N(1B)-C(3B)	-60.7(2)
C(9B)-C(8B)-N(1B)-C(3B)	-177.74(17)
C(1)-C(6)-O(1)-C(7)	178.9(2)
C(5)-C(6)-O(1)-C(7)	-1.8(3)
C(10)-C(9)-O(3)-C(14)	178.81(16)
C(8)-C(9)-O(3)-C(14)	79.75(19)
O(4)-C(14)-O(3)-C(9)	72.52(18)
C(15)-C(14)-O(3)-C(9)	-167.79(16)
O(3)-C(14)-O(4)-C(18)	-169.90(14)
C(15)-C(14)-O(4)-C(18)	70.68(18)
C(17)-C(18)-O(4)-C(14)	-58.8(2)
C(19)-C(18)-O(4)-C(14)	176.35(15)
C(15)-C(16)-O(5)-C(20)	-98.81(18)
C(17)-C(16)-O(5)-C(20)	22.14(19)
O(6)-C(20)-O(5)-C(16)	1.55(19)
C(21)-C(20)-O(5)-C(16)	118.44(17)
C(22)-C(20)-O(5)-C(16)	-117.72(17)
O(5)-C(20)-O(6)-C(17)	-26.79(17)
C(21)-C(20)-O(6)-C(17)	-144.84(15)
C(22)-C(20)-O(6)-C(17)	90.95(18)
C(18)-C(17)-O(6)-C(20)	162.94(15)

C(16)-C(17)-O(6)-C(20)	39.46(17)
C(1B)-C(6B)-O(1B)-C(7B)	10.7(3)
C(5B)-C(6B)-O(1B)-C(7B)	-169.6(2)
C(10B)-C(9B)-O(3B)-C(14B)	178.62(15)
C(8B)-C(9B)-O(3B)-C(14B)	81.9(2)
O(4B)-C(14B)-O(3B)-C(9B)	74.18(18)
C(15B)-C(14B)-O(3B)-C(9B)	-167.54(15)
O(3B)-C(14B)-O(4B)-C(18B)	-173.83(13)
C(15B)-C(14B)-O(4B)-C(18B)	69.05(18)
C(19B)-C(18B)-O(4B)-C(14B)	-179.08(14)
C(17B)-C(18B)-O(4B)-C(14B)	-54.0(2)
O(6B)-C(20B)-O(5B)-C(17B)	-30.63(19)
C(21B)-C(20B)-O(5B)-C(17B)	-148.52(17)
C(22B)-C(20B)-O(5B)-C(17B)	87.56(19)
C(18B)-C(17B)-O(5B)-C(20B)	164.38(16)
C(16B)-C(17B)-O(5B)-C(20B)	39.92(18)
C(15B)-C(16B)-O(6B)-C(20B)	-104.33(18)
C(17B)-C(16B)-O(6B)-C(20B)	16.5(2)
O(5B)-C(20B)-O(6B)-C(16B)	7.8(2)
C(21B)-C(20B)-O(6B)-C(16B)	125.33(17)
C(22B)-C(20B)-O(6B)-C(16B)	-111.77(18)

Symmetry transformations used to generate equivalent atoms:

Table 3.14: Hydrogen bonds for **166** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(7)-H(7)...O(2B)	0.84	1.98	2.804(2)	165.4
O(7B)-H(7B4)...O(4)	0.84	2.16	2.969(2)	161.6

Symmetry transformations used to generate equivalent atoms:

The absolute stereochemistry of peracetyl L-fucose-L-saccharosamine dissacharide **184** was confirm by single crystal X-ray analysis carried out on

crystals grown by slow solvent exchange at ambient temperature in a small open vial containing **184** and chloroform, which was placed upright inside a larger sealed vial containing hexanes; absolute structure parameter -0.1(2). The thermal ellipsoid diagram for dissacharide **184** is shown below:

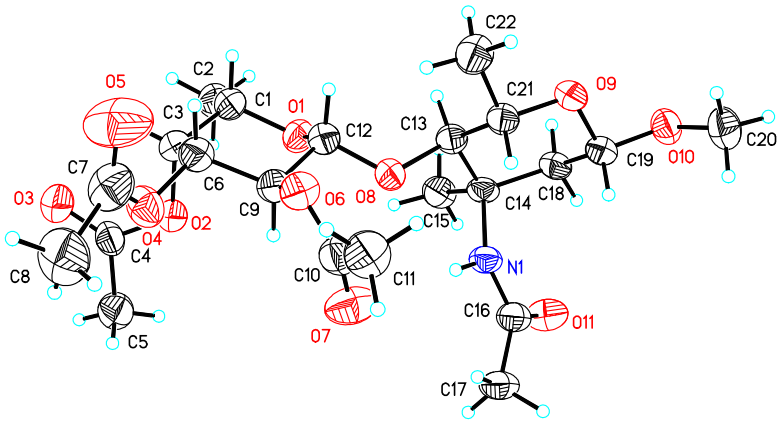


Table 3.15: Crystal data and structure refinement for **184**.

Identification code	b0673bs	
Empirical formula	C22 H35 N O11	
Formula weight	489.51	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.1737(7) Å	□= 90°.
	b = 10.9997(8) Å	□= 90°.
	c = 29.222(2) Å	□ = 90°.
Volume	2627.3(3) Å^3	
Z	4	
Density (calculated)	1.238 Mg/m^3	
Absorption coefficient	0.840 mm^{-1}	
F(000)	1048	
Crystal size	0.25 x 0.20 x 0.03 mm^3	
Theta range for data collection	3.02 to 64.46°.	

Index ranges	-8<=h<=6, -10<=k<=12, -32<=l<=28
Reflections collected	7946
Independent reflections	3685 [R(int) = 0.0230]
Completeness to theta = 64.46°	88.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9752 and 0.8175
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3685 / 0 / 319
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0404, wR2 = 0.0996
R indices (all data)	R1 = 0.0515, wR2 = 0.1072
Absolute structure parameter	-0.1(2)
Largest diff. peak and hole	0.481 and -0.149 e.$Å^{-3}$

Table 3.16: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for **184**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2527(4)	3543(3)	4117(1)	43(1)
C(2)	2070(4)	2240(3)	4010(1)	50(1)
C(3)	3935(4)	3650(3)	4452(1)	41(1)
C(4)	6046(4)	2139(3)	4521(1)	44(1)
C(5)	7577(4)	1705(3)	4302(1)	57(1)
C(6)	4418(4)	4966(3)	4515(1)	43(1)
C(7)	5928(6)	5803(4)	5143(1)	63(1)
C(8)	7631(6)	5870(4)	5343(1)	83(1)
C(9)	4745(4)	5532(3)	4053(1)	40(1)
C(10)	6342(4)	7276(3)	3867(1)	49(1)
C(11)	6525(5)	8600(3)	3963(1)	61(1)
C(12)	3288(4)	5368(3)	3743(1)	41(1)
C(13)	2570(4)	6056(2)	2967(1)	37(1)
C(14)	3270(3)	5497(2)	2527(1)	36(1)
C(15)	3156(4)	4111(2)	2540(1)	45(1)
C(16)	6056(4)	5688(3)	2158(1)	42(1)
C(17)	7796(4)	6020(3)	2262(1)	48(1)

C(18)	2318(4)	6002(2)	2117(1)	38(1)
C(19)	2179(4)	7359(2)	2135(1)	37(1)
C(20)	1414(5)	9017(3)	1670(1)	55(1)
C(21)	2311(4)	7435(2)	2942(1)	37(1)
C(22)	1357(5)	7921(3)	3348(1)	50(1)
N(1)	4998(3)	5888(2)	2504(1)	37(1)
O(1)	2949(3)	4115(2)	3686(1)	42(1)
O(2)	5343(3)	3018(2)	4266(1)	41(1)
O(3)	5505(3)	1789(2)	4880(1)	67(1)
O(4)	5894(3)	5036(2)	4783(1)	51(1)
O(5)	4750(4)	6348(3)	5271(1)	103(1)
O(6)	5093(3)	6794(2)	4117(1)	45(1)
O(7)	7145(3)	6703(2)	3599(1)	66(1)
O(8)	3763(3)	5843(2)	3321(1)	42(1)
O(9)	1369(2)	7736(2)	2542(1)	40(1)
O(10)	1251(3)	7751(2)	1761(1)	45(1)
O(11)	5645(3)	5270(2)	1786(1)	55(1)

Table 3.17: Bond lengths [Å] and angles [°] for **184**.

C(1)-O(1)	1.447(3)
C(1)-C(2)	1.513(4)
C(1)-C(3)	1.516(4)
C(3)-O(2)	1.450(4)
C(3)-C(6)	1.512(4)
C(4)-O(3)	1.203(4)
C(4)-O(2)	1.348(3)
C(4)-C(5)	1.483(5)
C(6)-O(4)	1.442(4)
C(6)-C(9)	1.508(4)
C(7)-O(5)	1.194(5)
C(7)-O(4)	1.349(4)
C(7)-C(8)	1.511(6)
C(9)-O(6)	1.429(4)
C(9)-C(12)	1.508(4)
C(10)-O(7)	1.200(4)

C(10)-O(6)	1.362(4)
C(10)-C(11)	1.491(5)
C(12)-O(8)	1.393(3)
C(12)-O(1)	1.416(3)
C(13)-O(8)	1.441(3)
C(13)-C(21)	1.534(4)
C(13)-C(14)	1.537(4)
C(14)-N(1)	1.478(4)
C(14)-C(15)	1.528(4)
C(14)-C(18)	1.532(4)
C(16)-O(11)	1.227(4)
C(16)-N(1)	1.350(4)
C(16)-C(17)	1.499(4)
C(18)-C(19)	1.498(4)
C(19)-O(10)	1.397(3)
C(19)-O(9)	1.422(3)
C(20)-O(10)	1.424(3)
C(21)-O(9)	1.439(3)
C(21)-C(22)	1.517(4)

O(1)-C(1)-C(2)	106.9(2)
O(1)-C(1)-C(3)	110.3(2)
C(2)-C(1)-C(3)	113.2(3)
O(2)-C(3)-C(6)	107.3(2)
O(2)-C(3)-C(1)	108.9(2)
C(6)-C(3)-C(1)	110.5(2)
O(3)-C(4)-O(2)	123.7(3)
O(3)-C(4)-C(5)	125.6(3)
O(2)-C(4)-C(5)	110.7(3)
O(4)-C(6)-C(9)	108.5(2)
O(4)-C(6)-C(3)	109.6(2)
C(9)-C(6)-C(3)	109.5(2)
O(5)-C(7)-O(4)	122.7(4)
O(5)-C(7)-C(8)	126.7(4)
O(4)-C(7)-C(8)	110.5(4)
O(6)-C(9)-C(6)	108.7(2)

O(6)-C(9)-C(12)	110.6(2)
C(6)-C(9)-C(12)	110.4(2)
O(7)-C(10)-O(6)	123.7(3)
O(7)-C(10)-C(11)	125.5(3)
O(6)-C(10)-C(11)	110.8(3)
O(8)-C(12)-O(1)	108.5(2)
O(8)-C(12)-C(9)	105.5(2)
O(1)-C(12)-C(9)	110.0(2)
O(8)-C(13)-C(21)	106.8(2)
O(8)-C(13)-C(14)	106.5(2)
C(21)-C(13)-C(14)	114.1(2)
N(1)-C(14)-C(15)	110.5(2)
N(1)-C(14)-C(18)	110.2(2)
C(15)-C(14)-C(18)	110.5(2)
N(1)-C(14)-C(13)	106.0(2)
C(15)-C(14)-C(13)	110.8(2)
C(18)-C(14)-C(13)	108.6(2)
O(11)-C(16)-N(1)	123.4(3)
O(11)-C(16)-C(17)	122.1(3)
N(1)-C(16)-C(17)	114.6(3)
C(19)-C(18)-C(14)	111.9(2)
O(10)-C(19)-O(9)	108.1(2)
O(10)-C(19)-C(18)	108.8(2)
O(9)-C(19)-C(18)	110.8(2)
O(9)-C(21)-C(22)	106.3(2)
O(9)-C(21)-C(13)	109.9(2)
C(22)-C(21)-C(13)	112.5(2)
C(16)-N(1)-C(14)	126.7(3)
C(12)-O(1)-C(1)	111.7(2)
C(4)-O(2)-C(3)	118.4(2)
C(7)-O(4)-C(6)	118.4(3)
C(10)-O(6)-C(9)	117.2(2)
C(12)-O(8)-C(13)	120.5(2)
C(19)-O(9)-C(21)	111.3(2)
C(19)-O(10)-C(20)	113.4(2)

Symmetry transformations used to generate equivalent atoms:

Table 3.18: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **184**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	39(2)	46(2)	45(2)	8(1)	3(1)	-3(1)
C(2)	43(2)	56(2)	52(2)	9(2)	-1(2)	-8(2)
C(3)	37(2)	47(2)	40(2)	5(1)	5(1)	3(1)
C(4)	42(2)	49(2)	40(2)	7(1)	-8(1)	1(1)
C(5)	58(3)	59(2)	53(2)	4(2)	2(2)	11(2)
C(6)	38(2)	51(2)	40(2)	-1(1)	-1(1)	0(1)
C(7)	71(3)	68(2)	48(2)	-15(2)	0(2)	-11(2)
C(8)	89(4)	88(3)	72(3)	-14(2)	-21(2)	-22(3)
C(9)	38(2)	39(2)	44(2)	1(1)	2(1)	0(1)
C(10)	42(2)	48(2)	56(2)	4(2)	-4(2)	-6(2)
C(11)	63(3)	48(2)	71(2)	1(2)	-5(2)	-9(2)
C(12)	35(2)	45(2)	44(2)	8(1)	2(1)	1(1)
C(13)	28(2)	38(2)	44(2)	6(1)	-3(1)	-7(1)
C(14)	24(2)	33(2)	51(2)	4(1)	0(1)	-6(1)
C(15)	40(2)	38(2)	58(2)	4(1)	-2(2)	-2(1)
C(16)	32(2)	34(2)	58(2)	3(1)	4(2)	0(1)
C(17)	32(2)	42(2)	69(2)	0(2)	8(2)	-2(1)
C(18)	28(2)	43(2)	43(2)	-1(1)	-3(1)	2(1)
C(19)	29(2)	41(2)	41(2)	1(1)	-2(1)	1(1)
C(20)	65(3)	42(2)	59(2)	10(2)	-5(2)	5(2)
C(21)	34(2)	38(2)	39(2)	3(1)	-2(1)	-3(1)
C(22)	60(2)	44(2)	46(2)	-1(1)	5(2)	3(2)
N(1)	26(1)	39(1)	48(2)	3(1)	1(1)	-3(1)
O(1)	42(1)	44(1)	41(1)	7(1)	1(1)	-6(1)
O(2)	42(1)	43(1)	39(1)	5(1)	1(1)	2(1)
O(3)	63(2)	84(2)	55(1)	26(1)	8(1)	15(1)
O(4)	52(2)	56(1)	45(1)	-6(1)	-11(1)	4(1)
O(5)	83(2)	134(3)	91(2)	-60(2)	13(2)	-3(2)
O(6)	48(2)	38(1)	50(1)	-3(1)	3(1)	-1(1)
O(7)	55(2)	54(1)	89(2)	-8(1)	22(2)	-9(1)

O(8)	33(1)	52(1)	43(1)	12(1)	-3(1)	-1(1)
O(9)	34(1)	40(1)	45(1)	4(1)	0(1)	6(1)
O(10)	45(1)	44(1)	45(1)	7(1)	-9(1)	0(1)
O(11)	44(2)	61(1)	59(1)	-12(1)	9(1)	-5(1)

Table 3.19: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **184**.

	x	y	z	U(eq)
H(1)	1570	3957	4245	52
H(2A)	1205	2229	3787	76
H(2B)	1709	1844	4284	76
H(2C)	3006	1821	3889	76
H(3)	3626	3294	4747	49
H(5A)	8451	2259	4370	85
H(5B)	7425	1661	3977	85
H(5C)	7845	913	4418	85
H(6)	3535	5408	4669	52
H(8A)	8162	6597	5237	125
H(8B)	8249	5173	5247	125
H(8C)	7564	5884	5671	125
H(9)	5699	5137	3915	48
H(11A)	7615	8853	3886	91
H(11B)	6325	8751	4281	91
H(11C)	5752	9048	3782	91
H(12)	2331	5800	3862	50
H(13)	1539	5654	3047	44
H(15A)	3674	3777	2273	68
H(15B)	2026	3871	2545	68
H(15C)	3694	3813	2810	68
H(17A)	8441	5293	2286	71
H(17B)	7840	6457	2546	71
H(17C)	8220	6521	2020	71
H(18A)	2866	5767	1836	46

H(18B)	1230	5649	2113	46
H(19)	3271	7724	2122	44
H(20A)	953	9474	1919	83
H(20B)	847	9213	1392	83
H(20C)	2551	9218	1638	83
H(21)	3376	7843	2926	44
H(22A)	1213	8783	3316	75
H(22B)	1948	7754	3625	75
H(22C)	306	7533	3361	75
H(1N)	5440(50)	6080(30)	2747(12)	62(12)

Table 3.20: Torsion angles [°] for **184**.

O(1)-C(1)-C(3)-O(2)	-61.9(3)
C(2)-C(1)-C(3)-O(2)	57.9(3)
O(1)-C(1)-C(3)-C(6)	55.7(3)
C(2)-C(1)-C(3)-C(6)	175.5(3)
O(2)-C(3)-C(6)-O(4)	-53.5(3)
C(1)-C(3)-C(6)-O(4)	-172.1(2)
O(2)-C(3)-C(6)-C(9)	65.3(3)
C(1)-C(3)-C(6)-C(9)	-53.3(3)
O(4)-C(6)-C(9)-O(6)	-64.3(3)
C(3)-C(6)-C(9)-O(6)	176.2(2)
O(4)-C(6)-C(9)-C(12)	174.3(2)
C(3)-C(6)-C(9)-C(12)	54.8(3)
O(6)-C(9)-C(12)-O(8)	63.8(3)
C(6)-C(9)-C(12)-O(8)	-175.9(2)
O(6)-C(9)-C(12)-O(1)	-179.4(2)
C(6)-C(9)-C(12)-O(1)	-59.1(3)
O(8)-C(13)-C(14)-N(1)	-45.5(3)
C(21)-C(13)-C(14)-N(1)	72.0(3)
O(8)-C(13)-C(14)-C(15)	74.5(3)
C(21)-C(13)-C(14)-C(15)	-168.0(2)
O(8)-C(13)-C(14)-C(18)	-163.9(2)
C(21)-C(13)-C(14)-C(18)	-46.4(3)
N(1)-C(14)-C(18)-C(19)	-66.7(3)

C(15)-C(14)-C(18)-C(19)	170.9(3)
C(13)-C(14)-C(18)-C(19)	49.1(3)
C(14)-C(18)-C(19)-O(10)	-178.0(2)
C(14)-C(18)-C(19)-O(9)	-59.3(3)
O(8)-C(13)-C(21)-O(9)	169.4(2)
C(14)-C(13)-C(21)-O(9)	52.0(3)
O(8)-C(13)-C(21)-C(22)	-72.4(3)
C(14)-C(13)-C(21)-C(22)	170.2(3)
O(11)-C(16)-N(1)-C(14)	9.2(4)
C(17)-C(16)-N(1)-C(14)	-170.8(3)
C(15)-C(14)-N(1)-C(16)	65.3(4)
C(18)-C(14)-N(1)-C(16)	-57.2(3)
C(13)-C(14)-N(1)-C(16)	-174.6(3)
O(8)-C(12)-O(1)-C(1)	177.0(2)
C(9)-C(12)-O(1)-C(1)	62.1(3)
C(2)-C(1)-O(1)-C(12)	175.9(3)
C(3)-C(1)-O(1)-C(12)	-60.6(3)
O(3)-C(4)-O(2)-C(3)	5.4(4)
C(5)-C(4)-O(2)-C(3)	-173.0(3)
C(6)-C(3)-O(2)-C(4)	115.9(3)
C(1)-C(3)-O(2)-C(4)	-124.5(3)
O(5)-C(7)-O(4)-C(6)	6.4(5)
C(8)-C(7)-O(4)-C(6)	-172.6(3)
C(9)-C(6)-O(4)-C(7)	109.9(3)
C(3)-C(6)-O(4)-C(7)	-130.6(3)
O(7)-C(10)-O(6)-C(9)	0.4(5)
C(11)-C(10)-O(6)-C(9)	178.6(3)
C(6)-C(9)-O(6)-C(10)	137.9(3)
C(12)-C(9)-O(6)-C(10)	-100.7(3)
O(1)-C(12)-O(8)-C(13)	74.5(3)
C(9)-C(12)-O(8)-C(13)	-167.7(2)
C(21)-C(13)-O(8)-C(12)	106.1(3)
C(14)-C(13)-O(8)-C(12)	-131.7(2)
O(10)-C(19)-O(9)-C(21)	-176.1(2)
C(18)-C(19)-O(9)-C(21)	64.8(3)
C(22)-C(21)-O(9)-C(19)	178.0(2)

C(13)-C(21)-O(9)-C(19)	-60.1(3)
O(9)-C(19)-O(10)-C(20)	76.2(3)
C(18)-C(19)-O(10)-C(20)	-163.5(3)

Symmetry transformations used to generate equivalent atoms:

Table 3.21: Hydrogen bonds for **184** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(8)	0.83(3)	2.18(4)	2.592(3)	110(3)

Symmetry transformations used to generate equivalent atoms:

4. References

1. Prescher, J. A.; Bertozzi, C. R. *Cell* **2006**, *126*, 851.
2. Ratner, D. M.; Adams, E. W.; Disney, M. D.; Seeberger, P. H. *ChemBioChem* **2004**, *5*, 1375.
3. von Itzstein, M. *Curr Opin Struc Biol* **2008**, *18*, 558.
4. Ritter, T. K.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3508.
5. Wolter, F.; Schoof, S.; Sussmuth, R. D. *Top. Curr. Chem.* **2007**, *267*, 143.
6. Kong, F.; Zhao, N.; Siegel, M. M.; Janota, K.; Ashcroft, J. S.; Koehn, F. E.; Borders, D. B.; Carter, G. T. *J. Am. Chem. Soc.* **1998**, *120*, 13301.
7. Singh, M. P.; Petersen, P. J.; Weiss, W. J.; Kong, F.; Greenstein, M. *Antimicrob. Agents Chemother.* **2000**, *44*, 2154.
8. Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, 99.
9. Wrodnigg, T. M.; Sprenger, F. K. *Mini-Reviews in Medicinal Chemistry* **2004**, *4*, 437.
10. Williams, J. D.; Sefton, A. M. *J. Antimicrob. Chemother.* **1993**, *31*, Suppl. C.
11. Busscher, G. F.; Rutjes, F. P. J. T.; van Delft, F. L. *Chem. Rev.* **2005**, *105*, 775.
12. Flatt, P. M.; Mahmud, T. *Nat. Prod. Rep.* **2007**, *24*, 358.
13. Begg, E. J.; Barclay, M. L. *Br. J. clin. Pharmac.* **1995**, *39*, 597.
14. Chu, M.; Mierzwa, R.; Patel, M.; Jenkins, J.; Das, P.; Pramanik, B.; Chan, T.-M. *Tetrahedron Lett.* **2000**, *41*, 6689.
15. Wagman, G. H.; Luedemann, G. M.; Weinstein, M. J. *Antimicrob. Agents Chemother.* **1964**, *10*, 33.
16. Weinstein, M. J.; Luedemann, G. M.; Oden, E. M.; Wagman, G. H. *Antimicrob. Agents Chemother.* **1964**, *10*, 24.
17. Belova, L.; Tenson, T.; Xiong, L.; McNicholas, P. M.; Mankin, A. S. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 3726.
18. McNicholas, P. M.; Najarian, D. J.; Mann, P. A.; Hesk, D.; Hare, P. S.; Shaw, K. J.; Black, T. A. *Antimicrob. Agents Chemother.* **2000**, *44*, 1121.
19. Hubbard, B. K.; Walsh, C. T. *Angew. Chem. Int. Ed.* **2003**, *42*, 730.
20. Vollmer, W.; Blanot, D.; de Pedro, M. A. *FEMS Microbiol. Res.* **2008**, *32*, 149.
21. Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2096.
22. Mackay, J. P.; Gerhard, U.; Beauregard, D. A.; Maplestone, R. A.; Williams, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4573.
23. Nagarajan, R. *J. Antibiot.* **1993**, *46*, 1181.
24. Gerhard, U.; Mackay, J. P.; Maplestone, R. A.; Williams, D. H. *J. Am. Chem. Soc.* **1993**, *115*, 232.
25. Nicas, T. I.; Mullen, D. L.; Flokowitsch, J. E.; Preston, D. A.; Snyder, N. J.; Zweifel, M. J.; Wilkie, S. C.; Rodriguez, M. J.; Thompson, R. C.; Cooper, R. D. *Antimicrob. Agents Chemother.* **1996**, *40*, 2194.
26. Guilmi, A. M.; Dessen, A.; Dideberg, O.; Vernet, T. *Curr. Pharma. Biotech.* **2002**, *3*, 63.
27. Halliday, J.; McKeveney, D.; Muldoon, C.; Rajaratnam, P.; Meutermans, W. *Biochem. Pharmacol.* **2006**, *71*, 957.
28. Welzel, P. *Chem. Rev.* **2005**, *105*, 4610.

29. Shi, S. D.-H.; Hendrickson, C. L.; Marshall, A. G.; Siegel, M. M.; Kong, F.; Carter, G. T. *J. Am. Soc. Mass. Spectrom.* **1999**, *10*, 1285.
30. Maki, M.; Renkonen, R. *Glycobiology* **2004**, *14*, 1R.
31. Madduri, K.; Waldron, C.; Merlo, D. J. *J. Bacteriol.* **2001**, *183*, 5632.
32. Ramos, A.; Lombo, F.; Brana, A. F.; Rohr, J.; Mendez, C.; Salas, J. A. *Microbiol.* **2008**, *154*, 781.
33. Chen, H.; Thomas, M. G.; Hubbard, B. K.; Losey, H. C.; Walsh, C. T.; Burkart, M. D. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 11942.
34. Hunt, A. H.; Molloy, R. M.; Debono, M.; Occolowitz, J. L. *Tetrahedron Lett.* **1988**, *29*, 1223.
35. Thibodeaux, C. J.; Melancon III, C. E.; Liu, H.-W. *Angew. Chem. Int. Ed.* **2008**, *47*, 9814.
36. Yoshida, Y.; Nakano, T.; Nezu, T.; Yamashita, Y.; Koga, T. *J. Biol. Chem.* **1999**, *274*, 16933.
37. Murakami, R.; Tomikawa, T.; Shin-Ya, K.; Shinozaki, J.; Kajiura, T.; Seto, H.; Hayakawa, Y. *J. Antibiotics* **2001**, *54*, 714.
38. Zhang, H.; White-Phillip, J. A.; Melancon III, C. E.; Kwon, H.-J.; Yu, W.-L.; Liu, H.-W. *J. Am. Chem. Soc.* **2007**, *129*, 14670.
39. Wang, L.; White, R. L.; Vining, L. C. *Microbiol.* **2002**, *148*, 1091.
40. Ishigami, K.; Hayakawa, Y.; Seto, H. *J. Antibiotics* **1994**, *47*, 1219.
41. Ishii, K.; Kondo, S.; Nishimura, Y.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiotics* **1983**, *36*, 451.
42. Nishimura, Y.; Ishii, K.; Kondo, S. *J. Antibiotics* **1990**, *43*, 54.
43. Berner, M.; Krug, D.; Bihlmaier, C.; Vente, A.; Muller, R.; Bechthold, A. *J. Bacteriol.* **2006**, *188*, 2666.
44. Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 4749.
45. Thang, T. T.; Winternitz, F.; Olesker, A.; Lagrange, A.; Lukacs, G. *J.C.S. Chem. Comm.* **1979**, 153.
46. Horton, D.; Weckerle, W. *Carbohydrate Res.* **1975**, *44*, 227.
47. Brimacombe, J. S.; Rahman, K. M. M. *J. Chem. Soc. Perkin Trans. I* **1985**, 1073.
48. Funabashi, M.; Hong, N.-G.; Kodama, H.; Yoshimura, J. *Carbohydrate Res.* **1978**, *67*, 139.
49. Sato, K.; Miyama, D.; Akai, S. *Tetrahedron Lett.* **2004**, *45*, 1523.
50. Giuliano, R. M.; Deisenroth, T. W.; Frank, W. C. *J. Org. Chem.* **1986**, *51*, 2304.
51. Dyong, I.; Schulte, G. S. *Chem. Ber.* **1981**, *114*, 1484.
52. Greven, R.; Jutten, P.; Scharf, H.-D. *J. Org. Chem.* **1993**, *58*, 3742.
53. Roth, W.; Pigman, W. *Meth. Carbohydr. Chem.* **1963**, *2*, 407.
54. Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Vega, J. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2525.
55. Doi, T.; Shibata, K.; Kinbara, A.; Takahashi, T. *Chem. Lett.* **2007**, *36*, 1372.
56. Noecker, L.; Duarte, F.; Bolton, S. A.; McMahon, W. G.; Diaz, M. T.; Giuliano, R. M. *J. Org. Chem.* **1999**, *64*, 6275.
57. Cutchins, W. W.; McDonald, F. E. *Org. Lett.* **2002**, *4*, 749.
58. Parker, K. A.; Chang, W. *Org. Lett.* **2005**, *7*, 1785.
59. McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675.
60. McDonald, F. E.; Zhu, H. Y. H. *Tetrahedron* **1997**, *53*, 11061.

61. McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246.
62. McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304.
63. Koo, B.; McDonald, F. E. *Org. Lett.* **2007**, *9*, 1737.
64. Parker, K. A.; Chang, W. *Org. Lett.* **2003**, *5*, 3891.
65. Davidson, M. H.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 1601.
66. Moilanen, S. B.; Tan, D. S. *Org. Biomol. Chem.* **2005**, *3*, 798.
67. Wipf, P.; Graham, T. H. *J. Org. Chem.* **2003**, *68*, 8798.
68. Fei, Z.; McDonald, F. E. *Org. Lett.* **2007**, *9*, 3547.
69. Nowroozi-Isfahani, T.; Musaev, D. G.; McDonald, F. E.; Morokuma, K. *Organometallics* **2005**, *24*, 2921.
70. Sordo, T.; Campomanes, P.; Dieguez, A.; Rodriguez, F.; Fananas, F. J. *J. Am. Chem. Soc.* **2004**, *127*, 944.
71. Barluenga, J.; Dieguez, A.; Rodriguez, F.; Fananas, F. J.; Sordo, T.; Campomanes, P. *Chem. Eur. J.* **2005**, *11*, 5735.
72. Sheng, Y.; Musaev, D. G.; Reddy, K. S.; McDonald, F. E.; Morokuma, K. *J. Am. Chem. Soc.* **2002**, *124*, 4149.
73. Sangu, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* **2004**, *6*, 353.
74. McDonald, F. E.; Reddy, K. S. *J. Organomet. Chem.* **2001**, *617-618*, 444.
75. Danishefsky, S. L.; Bilodeau, M. T. *Angew. Chem. Int. Ed.* **1996**, *35*, 1380.
76. Danishefsky, S. L.; Roberge, J. Y. *Pure & Appl. Chem.* **1995**, *67*, 1647.
77. Seeberger, P. H.; Danishefsky, S. L. *Acc. Chem. Res.* **1998**, *31*, 685.
78. Boone, M. A.; McDonald, F. E.; Lichter, J.; Lutz, S.; Cao, R.; Hardcastle, K. I. *Org. Lett.* **2009**, *11*, 851.
79. McDonald, F. E.; Reddy, K. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3653.
80. Schmidt, R. R. *Pure & Appl. Chem.* **1989**, *61*, 1257.
81. Schmidt, R. R.; Castro-Palomino, J. C.; Retz, O. *Pure & Appl. Chem.* **1999**, *71*, 729.
82. Schmidt, R. R.; Wegmann, B.; Jung, K.-H. *Liebigs Ann. Chem.* **1991**, 121.
83. Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Galarza, R.; Legido, M.; Urchegui, R.; Roman, P.; Luque, A.; Server-Carrio, J.; Linden, A. *J. Org. Chem.* **1997**, *62*, 2070.
84. Schmidt, R. R.; Michel, J. *Tetrahedron Lett.* **1984**, *25*, 821.
85. Schmidt, R. R.; Michel, J. *Liebigs Ann. Chem.* **1984**, 1343.
86. Imamoto, T. *Pure & Appl. Chem.* **1990**, *62*, 747.
87. Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.
88. Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.
89. Hutchins, R. O. *J. Org. Chem.* **1993**, *58*, 2920.
90. Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763.
91. Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jap.* **1967**, *40*, 2380.
92. Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M. *Eur. J. Org. Chem.* **2005**, 2867.
93. Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.
94. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.
95. Bourgeois, D.; Prunet, J.; Pancrazi, A.; Prange, T.; Lallemand, J.-Y. *Eur. J. Org. Chem.* **2000**, 4029.

96. Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586.
97. Kirby, A. J.; Evans, C. M. *J. Chem. Soc. Perkin Trans. II* **1984**, 1269.
98. Caylay, A. *Synlett* **2007**, 339.
99. Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.
100. Faure, R.; Shiao, T. C.; Damerval, S.; Roy, R. *Tetrahedron Lett.* **2007**, *48*, 2385.
101. Hanashima, S.; Castagner, B.; Esposito, D.; Nokami, T.; Seeberger, P. H. *Org. Lett.* **2007**, *9*, 1777.
102. Hayashi, M.; Tanaka, M.; Itoh, M.; Miyauchi, H. *J. Org. Chem.* **1996**, *61*, 2938.
103. Nicolaou, K. C.; Cho, S. Y.; Hughes, R.; Winssinger, N.; Smethurst, C.; Labischinski, H.; Endermann, R. *Chem. Eur. J.* **2001**, *7*, 3798.
104. Katz, T. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3010.
105. Maeyama, K.; Iwasawa, N. *J. Org. Chem.* **1999**, *64*, 1344.
106. Babu, S. R.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428.
107. Guo, H.; O'Doherty, G. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 5206.
108. Parker, K. A.; Meschwitz, S. M. *Carbohydrate Res.* **1988**, *172*, 319.
109. Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570.
110. Pihko, A. J.; Nicolaou, K. C.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **2001**, *12*, 937.
111. Handa, M.; III, S. W. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1036.
112. Cipollone, A.; Berettoni, M.; Bigioni, M.; Binaschi, M.; Cermele, C.; Monteagudo, E.; Olivieri, L.; Palomba, D.; Animati, F.; Goso, C.; Maggi, C. A. *Bioorg. Med. Chem.* **2002**, *10*, 1459.
113. Halcomb, R. L.; Boyer, S. H.; Danishefsky, S. L. *Angew. Chem. Int. Ed.* **1992**, *31*, 338.
114. Morton, G. E.; Barrett, A. G. M. *Org. Lett.* **2006**, *8*, 2859.
115. Sugiyama, T.; Murayama, T.; Yamashita, K. *Tetrahedron Lett.* **1990**, *31*, 7343.
116. Chiba, S.; Kitamura, M.; Narasaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6931.
117. Komarova, B. S.; Tsvetkov, Y. E.; Knirel, Y. A.; Zahringer, U.; Pier, G. B.; Nifantiev, N. E. *Tetrahedron Lett.* **2006**, *47*, 3583.
118. Tsai, T. Y. R.; Jin, H.; Wiesner, K. *Can. J. Chem.* **1984**, *62*, 1403.
119. Russell, G. D.; Danishefsky, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 3471.
120. Reetz, M. T. *Angew. Chem. Int. Ed.* **1984**, *23*, 556.
121. Corey, E. J.; Ponder, J. W.; Ulrich, P. *Tetrahedron Lett.* **1980**, *21*, 137.
122. Fisyuk, A. S.; Vorontsova, M. A. *Chem. Heterocycl. Compd.* **1998**, *34*, 629.
123. Schmidt, R. R. *Synthesis* **1972**, 333.
124. Wohl, K. *Chem. Ber.* **1901**, *34*, 1914.
125. Lora-Tamayo, M.; Madronero, R.; Munoz, G. G.; Leipprand, H. *Chem. Ber.* **1964**, *97*, 2234.
126. Lora-Tamayo, M.; Madronero, R.; Gomez-Parra, V. *An. Soc. Esp. Fis. Quim.* **1966**, *256*, 4239.
127. Schmidt, R. R. *Chem. Ber.* **1965**, *98*, 334.
128. Jochims, J. C.; Abu-El-Halawa, R.; Glocker, M. O.; Zsolnai, L.; Huttner, G. *Synthesis* **1990**, 763.
129. Ghera, E.; Maurya, R.; Hassner, A. *Tetrahedron Lett.* **1989**, *30*.
130. Huang, S.; Pan, Y.; Zhu, Y.; Wu, A. *Org. Lett.* **2005**, *7*, 3797.

131. Burger, K.; Huber, E.; Schotag, W.; Ottlinger, R. *J. Chem. Soc., Chem. Commun.* **1983**, 945.
132. Shimizu, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **2000**, *41*, 5715.
133. Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1989**, *45*, 4627.
134. Mitasev, B.; Brummond, K. M. *Synlett* **2006**, 3100.
135. Funk, R. L.; Abelman, M. M. *J. Org. Chem.* **1986**, *51*, 3248.
136. Kashima, C.; Imada, S.; Nishio, T. *Chem. Lett.* **1978**, 1391.
137. Auricchio, S.; Vaina De Pava, O.; Vera, E. *Synthesis* **1979**, 116.
138. Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437.
139. Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175.