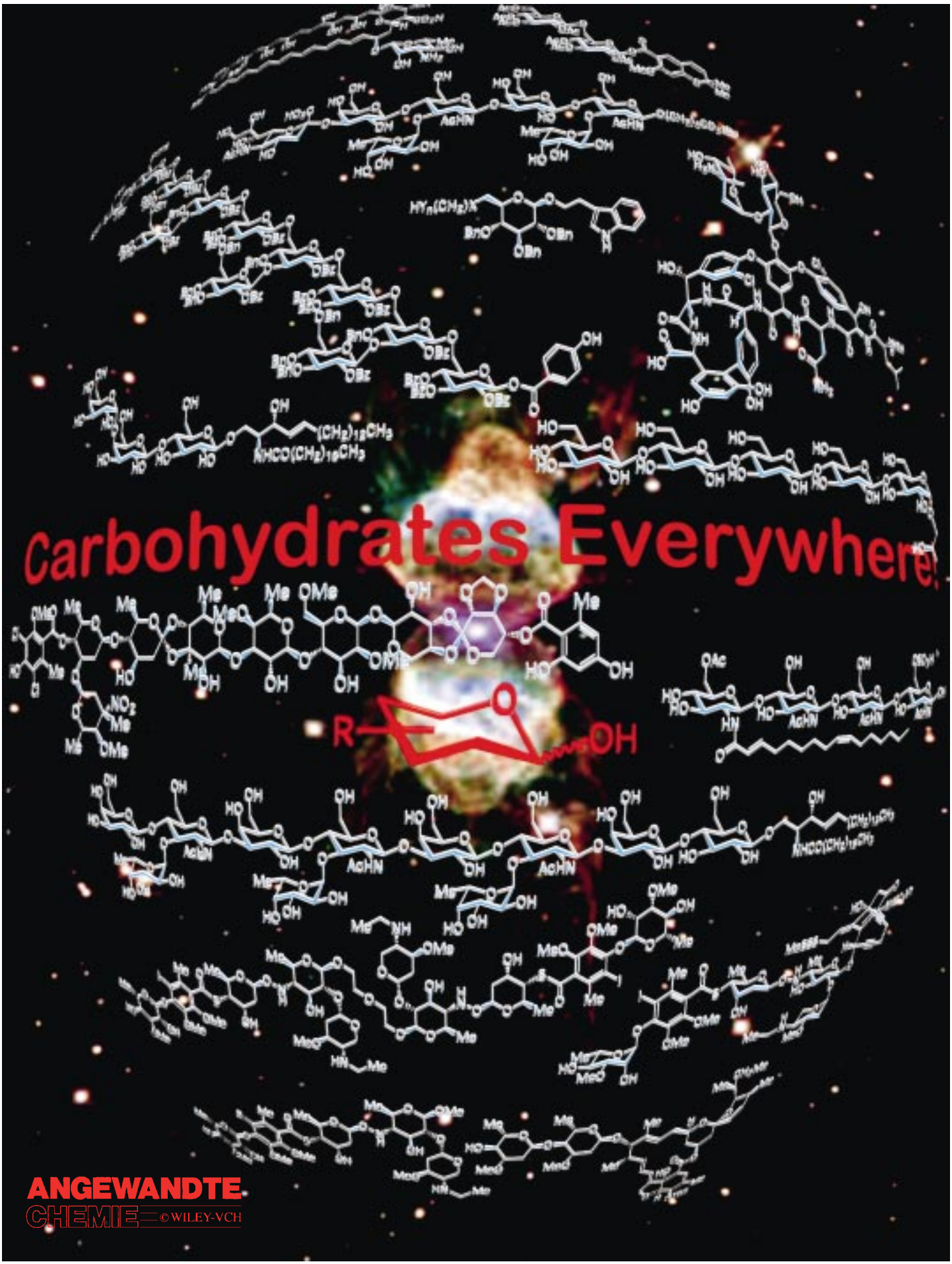

The “ant nebula” (menzel 3) is shown in the background of the picture. (Reproduced with permission from NASA, ESA, and the Hubble Heritage team (STSci/AURA).) We thank R. Sahai (Jet Propulsion Lab) and B. Balick (University of Washington) for the graphical arrangement.

Adventures in Carbohydrate Chemistry: New Synthetic Technologies, Chemical Synthesis, Molecular Design, and Chemical Biology**

K. C. Nicolaou* and Helen J. Mitchell

In memory of Telemachos Charalambous

The field of carbohydrate chemistry has occupied the minds and hearts of many scientists for over a hundred years and, as we enter the twenty-first century, it continues to be both vigorous and challenging. Among the most exciting aspects of organic chemistry in the last few decades has been the interplay between the specialized subdisciplines of carbohydrate chemistry and total synthesis, each enabling and advancing the other in new directions and towards greater heights. In this review article we highlight our own adventures at the interface of these disciplines, which were driven for the most part by objectives in chemical synthesis and chemical biology. Specifically, we describe our interests and efforts to utilize carbohydrates as starting materials for total synthesis, to invent and develop new synthetic technologies for carbohydrate synthesis, to construct complex oligosaccharides in solution or on solid support, and to utilize carbohydrate templates as scaffolds for peptide mimetics and for molecular diversity construction. Finally, applications of the developed synthetic strategies and enabling technologies towards the solution of biologically significant problems are discussed.

Keywords: carbohydrates · glycosidation · natural products · synthetic methods · total synthesis

1. Introduction

The abundance of carbohydrates in nature and their diverse roles in biological systems make them attractive as subjects for chemical and biological research. They are found as monomers, oligomers, or polymers, or as components of biopolymers and other naturally occurring substances. As domains of natural products, they play important roles in conferring certain physical, chemical, and biological properties to their carrier molecules. Furthermore, they have been implicated in many cellular processes, including cell–cell recognition, cellular transport, and adhesion; they appear in all cells in some form or another, for example, as peptido- and proteoglycans, glycoproteins, nucleic acids, lipopolysaccharides, or glycolipids.[1a] Due to their importance as building blocks, synthetic targets, and biological tools, and their potential as drug candidates, investigations into these compounds have been on the rise for some time. In this review we will recount our experiences with carbohydrates which have, for the most part, focused on new synthetic technologies, molecular design, and chemical biology studies. Our work in the carbohydrate arena has been inspired by many researchers in the field: To name but two, Stephen Hanessian[1b] was the first to inspire this group in using carbohydrates as templates for total synthesis and Sam Danishefsky[1c] encouraged and supported us to sustain an interest in carbohydrate chemistry.

Before we discuss our adventures in the carbohydrate area we shall briefly mention a selected number of glycosidation methods (see Scheme 1),[2] many of which are found throughout the schemes that follow, because of their centrality within carbohydrate chemistry. The earliest known glycosidation method is that of Koenigs and Knorr[3] (Scheme 1a), which was first reported a century ago. This reaction involves the coupling of a glycosyl bromide or chloride with a hydroxy component upon activation of the former with a heavy metal ion, typically silver or mercury.[4]

In most glycosidation reactions, the resulting anomeric stereochemistry is controlled by the nature of the C2

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[**] A list of abbreviations can be found at the end of this article. Telemachos Charalambous was an inspiring teacher at the Pancyprian Gymnasium, Nicosia, Cyprus.

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substituent. Thus, when the C2 oxygen is protected with an alkyl or benzyl group the anomeric effect dominates and the α-anomer is preferentially formed (Scheme 1b). The same configuration is obtained with 2-deoxyglycosyl donors. However, when the C2 position is occupied by a participating group such as an ester (Scheme 1c), a phenylthio, or a phenylseleno group (see below), the stereochemical outcome is opposite to that of the C2 substituent (either α or β) and a 1,2-*trans* product is formed.[5] Extensions of the Koenigs–Knorr conditions include the use of Lewis acids and phase-transfer catalysis[6] to activate the anomeric halides.

Glycosyl fluorides, while known since 1923, were first introduced as glycosyl donors in 1981 by the Mukaiyama group (Scheme 1d).[7] This method has found widespread applications due to a number of advantages associated with glycosyl fluorides. They are usually more stable than other halides and can often be purified by chromatography. In addition, they exhibit considerable thermal and chemical stability. Glycosyl fluorides are accessible from lactols through the action of DAST,[8a] HF · py,[8b] 2-fluoro-1-methylpyridinium tosylate,[8c] hexafluoropropene,[8d] Ph_3P/DEAD/Et_3OBF_4,[8e] and Selectfluor.[8f] Glycosyl fluorides have also been prepared from thioglycosides by treatment with NBS/DAST (Scheme 1f) and NBS/HF · py.[9] They are activated by exposure to fluorophiles such as Lewis acids,[10, 11] silver salts, and various metallocenes.[12]

The trichloroacetimidate-mediated glycosidation procedure (Scheme 1g) reported by Schmidt et al.[13] in 1980 is a very powerful method and it has been widely used in complex molecule construction. The trichloroacetimidate donors are easily prepared from lactols and trichloroacetonitrile in the presence of a base such as NaH or DBU. They are activated by acids, usually Lewis acids such as TMSOTf[14] or $BF_3 \cdot Et_2O$.[13] *O*-Acyl glycosyl donors, particularly the *O*-acetyl glycosyl donor (Scheme 1h), are easily accessible, and they have been used extensively in glycosidation reactions upon activation with Lewis acids.[15] Thioglycosides, particularly phenylthio- and ethylthioglycosides (Scheme 1i), have been widely applied in glycosidation and related reactions due to their ease of formation, relative stability to various reaction conditions, and convenient activation with electrophilic reagents[16] or oxidizing agents. Glycosidations with *O*-silylated glycosyl derivatives,[17] in the presence of TMSOTf as a catalyst, have been implemented (Scheme 1j). As first demonstrated by Kahne et al.,[18a] glycosyl phenylsulfoxides act as mild glycosyl donors upon activation with Tf_2O (Scheme 1k). Recent advances along these lines have led to a sulfoxide-based method for forming β-mannosides.[18b]

A related method is the direct conversion of lactols into glycosides with alcohols, Ph_2SO, and Tf_2O by Gin and co-workers (Scheme 1l).[19] Glycals have been employed as versatile intermediates in glycosidation reactions.[20] Thus, a number of electrophiles such as $I(col)_2ClO_4$,[21] NIS,[22] PhSeCl,[23] PhSCl, and NBS[24] (Scheme 1m) have been utilized to induce coupling of glycals with hydroxy components and to produce, after reductive removal of the resulting C2 substituent, 2-deoxyglycosides. Wong and co-workers[25] have recently introduced a method for the synthesis of 2-fluorosugars by exposing glycals to Selectfluor (Scheme 1m).

Halcomb and Danishefsky used glycals extensively by opening the epoxide that is formed as an intermediate by exposure of various glycals to DMDO (Scheme 1n).[26] The use of *n*-pentenyl glycosides as glycosyl donors, introduced by Fraser-Reid et al.,[27] involves activation with an electrophile, followed by expulsion of the anomeric substituent and trapping of the incipient oxonium species with a hydroxy component (Scheme 1o). Glycosyl phosphates[28a] and phos-

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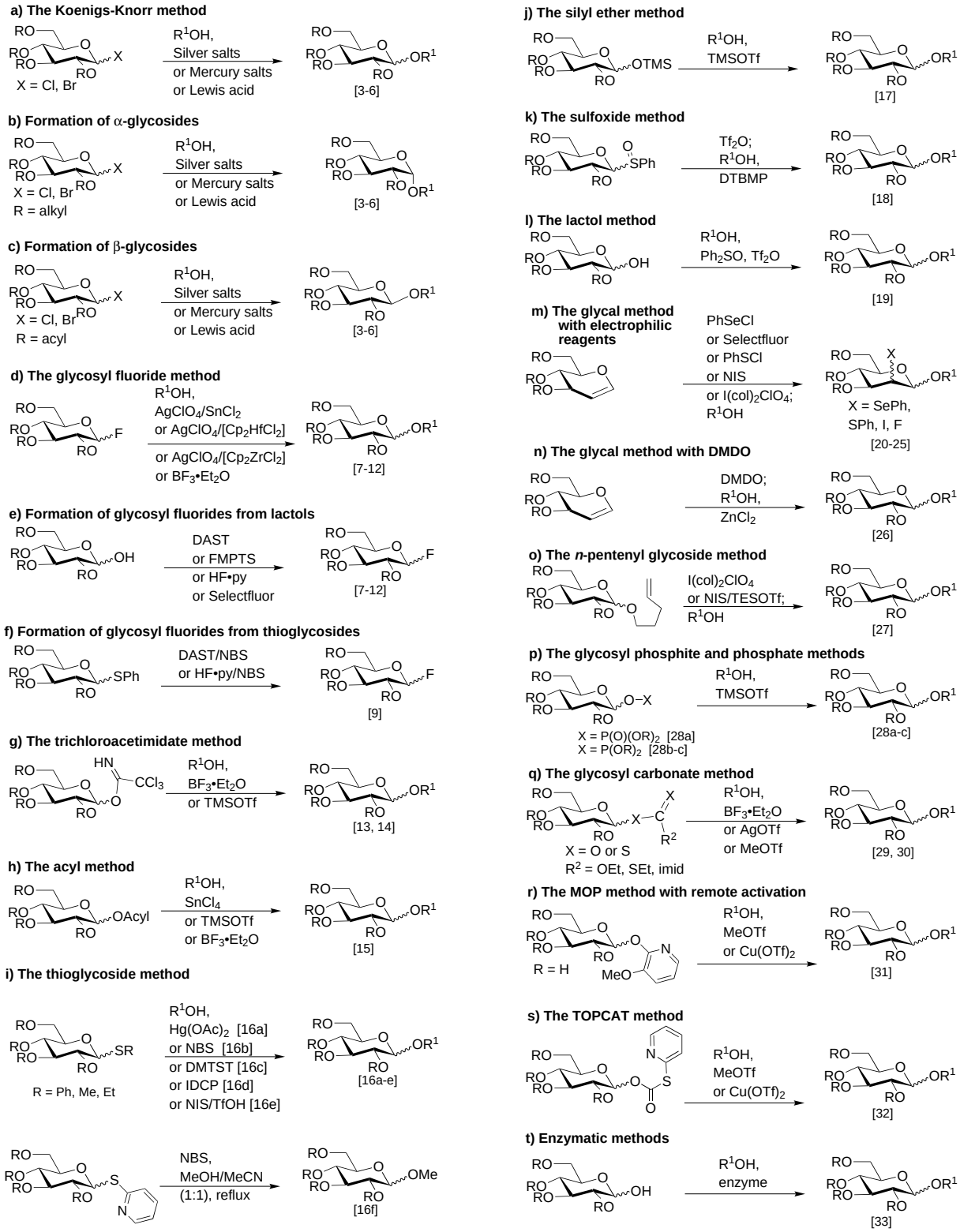
Helen J. Mitchell was born in London in 1971. She received her BSc degree from the University of Victoria, BC, Canada, and her PhD under the guidance of Professor K. C. Nicolaou from the University of California, San Diego, where she worked on the synthesis of complex natural products including the total synthesis of the oligosaccharide antibiotic everninomicin 13,384-1 and the final stages in the total synthesis of vancomycin. She is currently continuing her studies into the synthesis of natural products with Professor K. C. Nicolaou as a postdoctoral fellow at The Scripps Research Institute. Her research interests include natural products synthesis and carbohydrate chemistry, and the application of these fields to chemical biology.



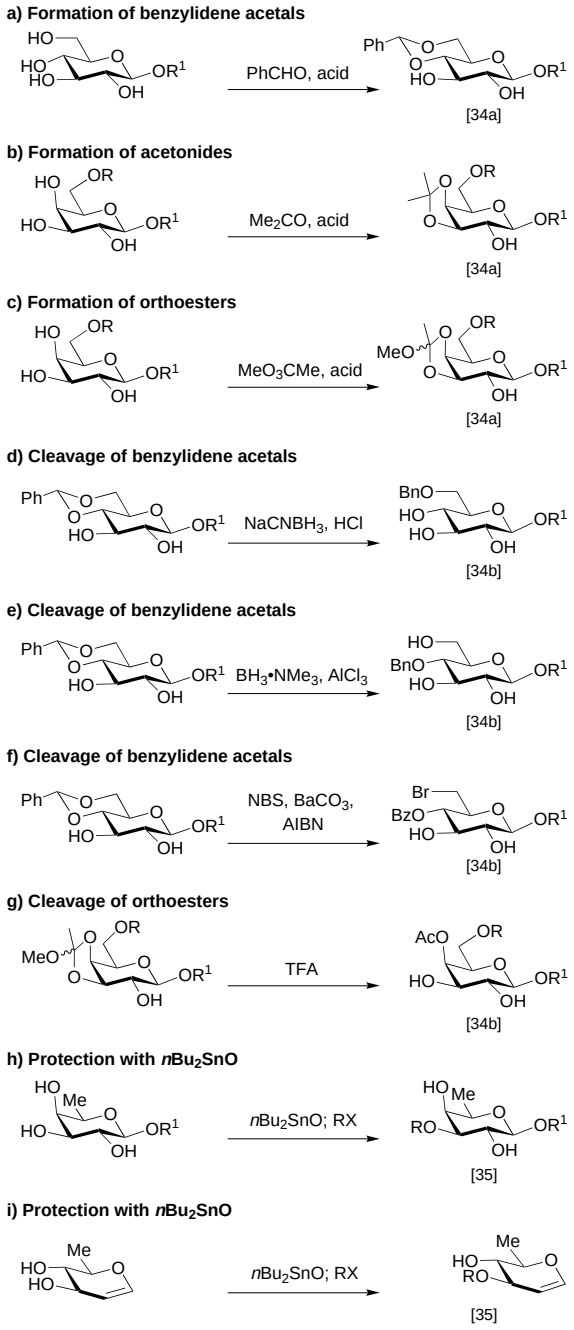
Scheme 1. General glycosidation methods. (Numbers in square brackets are literature references.)

phites[28b, c] have been successfully employed in glycosidation reactions upon activation with TMSOTf (Scheme 1p). Various carbonate-type donors, including xanthates[29] and imidazole thiocarbamates,[30] have been used in glycoside-forming reactions with alcohols after activation with methylating agents (Scheme 1q). Hanessian and co-workers have developed the remote activation approach to oligosaccharides through unprotected and protected MOP glycosyl donors in the presence of catalytic amounts of methylating agents or cupric salts (Scheme 1r).[31] Hanessian and co-workers have also employed 2-thiopyridylcarbonate sugar derivatives as donors to form glycosides upon activation with methylating

agents or $Cu(OTf)_2$ (Scheme 1s).[32] Finally, one should note the numerous successes in enzymatic glycosidations[33] through the use of glycosidases, and glycosyl transferases and UDP-protected sugars (Scheme 1t).

At this time we also mention several very useful reactions involving the regioselective functionalization of polyol-containing mono- and oligosaccharides, as depicted in Scheme 2, which can be found throughout the syntheses to be presented. In short, these reactions involve the selective formation of acetals and orthoesters, the selective cleavage of acetals and orthoesters, and the monoprotection of polyols mediated by tin acetals. The condensation of aldehydes and ketones with carbohydrates in the presence of Lewis or protic acids to form acyclic and cyclic acetals is found in many monosaccharide syntheses;[34a] the most common of which is the 4,6-*O*-benzylidene acetal, shown in Scheme 2a for D-glucose. The 3,4-*O*-isopropylidene (Scheme 2b) and 3,4-*O*-orthoester (Scheme 2c) are also frequently used to funtionalize D-galactose (shown), as well as other derivatives.

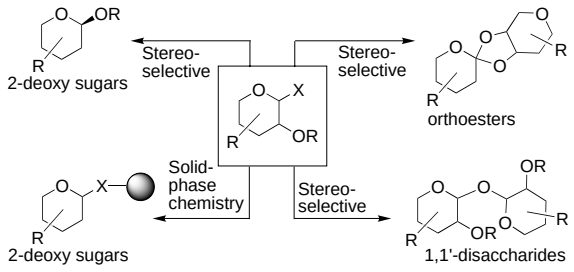
The selective cleavage of the 4,6-*O*-benzylidene group with various reagents allows entry into three types of structures.[34b] Treatment of the 4,6-*O*-benzylidene group with $NaCNBH_3$ and HCl (Scheme 2d) affords the 6-*O*-benzyl derivative, while exposure to $BH_3 \cdot NMe_3$ (Scheme 2e) furnishes the 4-*O*-benzyl derivative. Finally, treatment of the 4,6-*O*-benzylidene group with NBS, $BaCO_3$, and AIBN affords the 6-*O*-bromo-4-*O*-benzoyl derivative through radical cleavage (Scheme 2f), which easily leads to deoxygenation of the C6 position. The 3,4-*O*-orthoester of D-galactose can also be cleaved to afford the 4-*O*-acetate upon exposure to TFA (Scheme 2g). The regioselective acylation and alkylation of tin acetals[35] is very useful for the selective protection of a number of polyol-containing systems, including protection of equatorial over axial hydroxyl groups (Scheme 2h) and for differentiation between two equatorial hydroxyl groups with different steric environments (Scheme 2i). While this list is by no means exhaustive, it highlights just a few of the efficient methods used in the syntheses below.



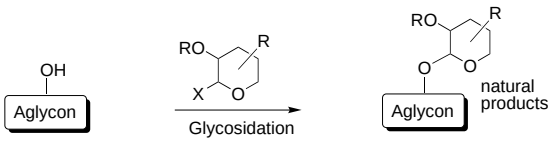
Scheme 2. Regioselective methods for protection.

In our dealings with carbohydrates we were faced with a number of challenges and objectives. In some instances our encounters focused purely on utilizing carbohydrates as starting materials for the total synthesis of complex, non-glycosidic natural products (see Scheme 3). In these endeavors we were decisively influenced by many others, but most notably by Stephen Hanessian, whose pioneering works in the field were both inspiring and exemplary. In other instances, we were challenged by difficult glycosidations for which new synthetic methods had to be developed (see Scheme 4) or new strategies had to be designed before success. Goals in these efforts varied from attaching a single carbohydrate unit onto a complex aglycon system of a natural product (see Scheme 5) to the construction of complex, naturally occurring carbohy-

Scheme 3. Carbohydrate templates as starting materials for the construction of complex molecules.

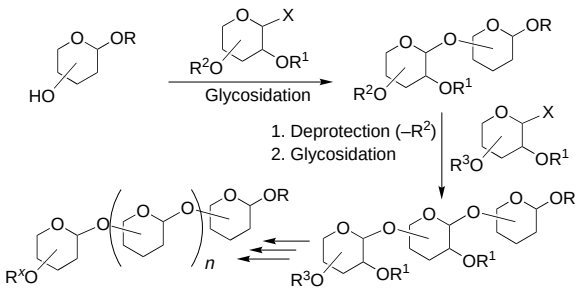


Scheme 4. New synthetic technologies in carbohydrate chemistry.



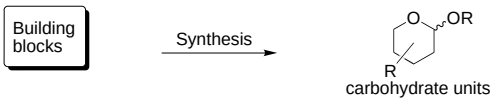
Scheme 5. Glycosidations of aglycons in the formation of natural products.

drates from simple building blocks and monosaccharides (see Scheme 6). Yet in other circumstances the need was to efficiently construct rare or difficult to access carbohydrate



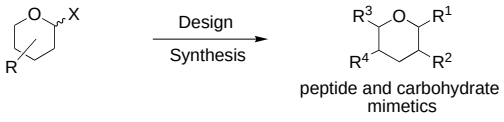
Scheme 6. Synthesis of complex oligosaccharides from simple building blocks and monosaccharides.

moieties for incorporation into larger structures as building blocks (see Scheme 7). Finally, designed carbohydrates or molecules based on carbohydrate templates were the objects



Scheme 7. New methods for the construction of carbohydrate units.

of investigation (see Scheme 8). In all of these endeavors, new chemistry or biology was the ultimate goal. In the following pages we describe these adventures, highlighting the enabling technologies that were developed along the way and the chemical biology investigations that were facilitated at the end.



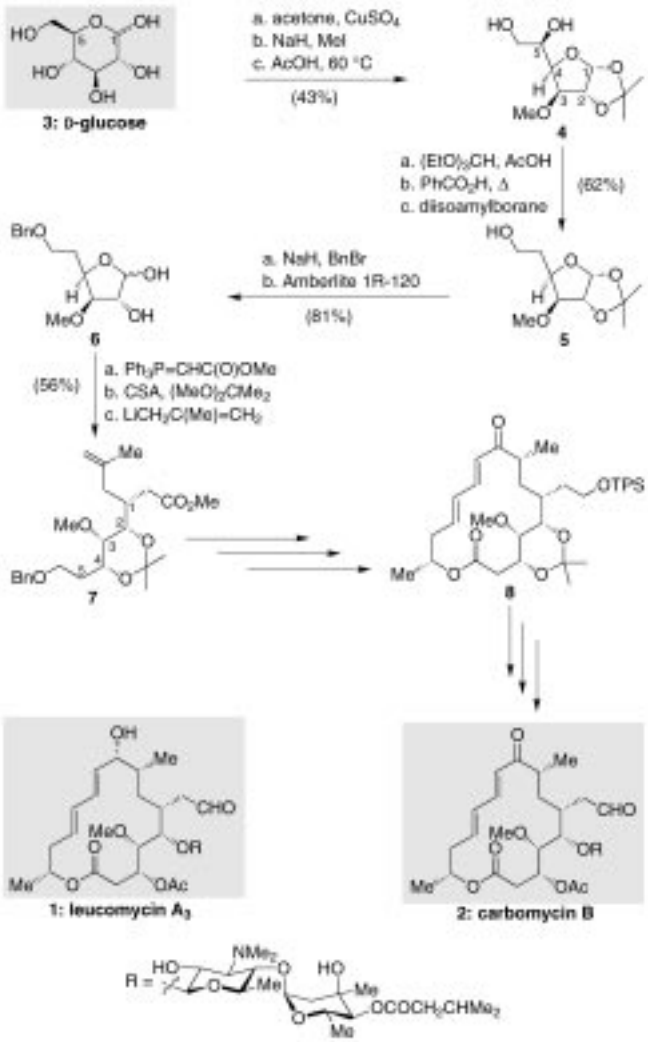
Scheme 8. Design and synthesis of peptide and carbohydrate mimetics.

2. Carbohydrates as Starting Materials for Total Synthesis

Rich in functionality and stereochemistry, carbohydrates are excellent starting materials for total synthesis. This realization goes back decades and is, by no means, our invention. The examples from our group discussed below, however, are demonstrative of the concept and strongly support the notion of the carbohydrate "chiral pool" as a valuable source of diverse building blocks for organic synthesis. Given the renewable nature of this source, the importance of carbohydrates in synthesis is bound to increase in the future. Advantages of using carbohydrates as starting materials include their known absolute stereochemistry, their often low cost, and their synthetic fertility. Their usefulness expands with increased ability by which synthetic chemists are able to manipulate them into new materials, which often bear little, if any, resemblance to the original structures. Imaginative ways to carry out such transformations are the trademark of elegant carbohydrate-based syntheses. The order of the following cases from these laboratories is chronological.

2.1. Leucomycin A_3 and Carbomycin B

Leucomycin A_3 (**1**, Scheme 9) and carbomycin B (**2**) represent two clinically important 16-membered ring macrolide antibiotics. The semisynthesis of these macrolides from D-glucose (**3**), chosen because it contained three of the required stereocenters, was reported by this group in 1981, and is shown in Scheme 9.[36–40] Thus, D-glucose (**3**) was converted into the 1,2;5,6-bisacetonide, followed by C3 methylation and cleavage to form diol **4**. Formation of the orthoester,

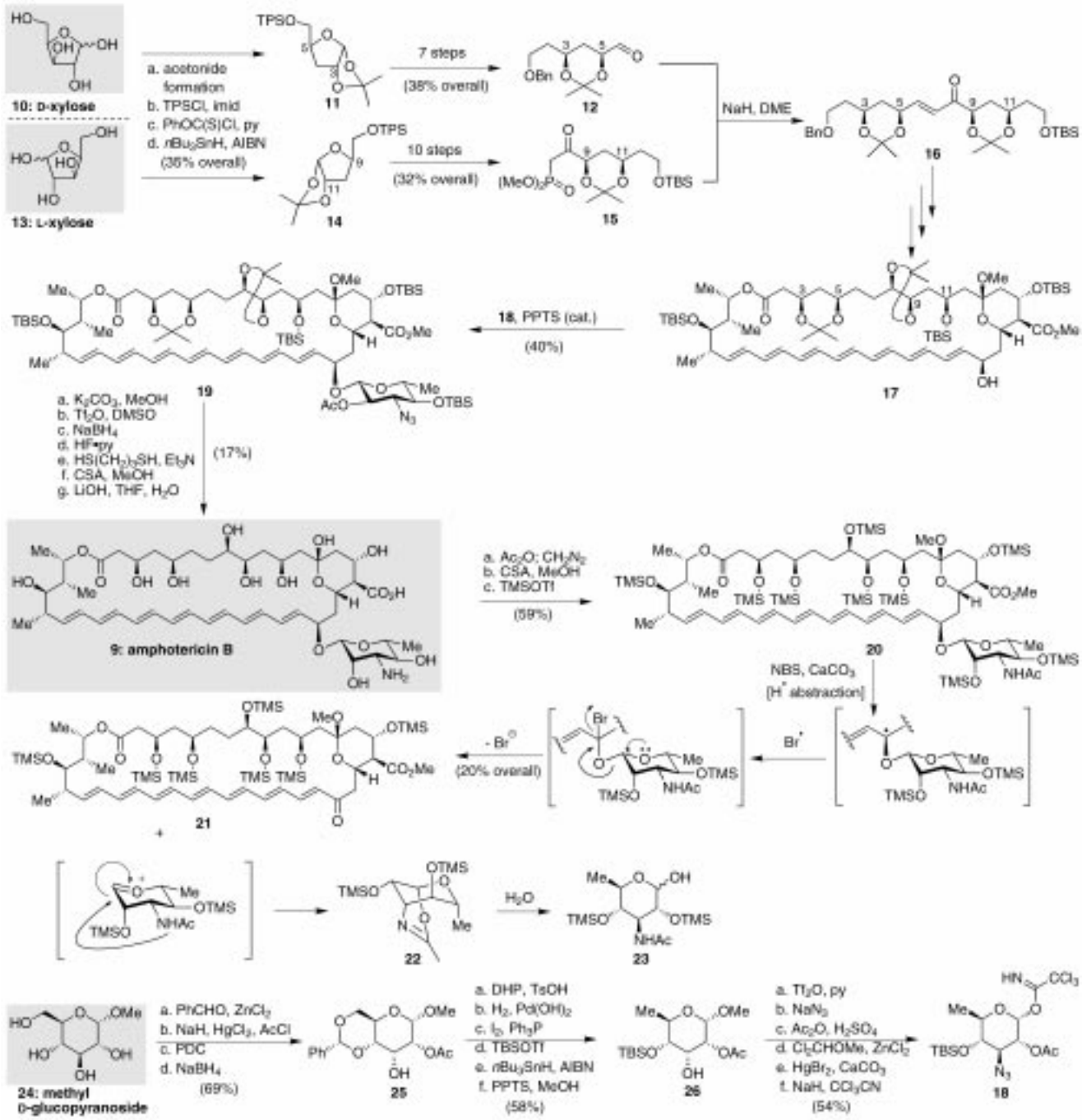


Scheme 9. Semisynthesis of leucomycin A_3 (**1**) and carbomycin B (**2**) from D-glucose (**3**) (1981).[36–40]

heating in the presence of benzoic acid and, finally, hydroboration of the resulting olefin with diisoamylborane furnished primary alcohol **5** in 27% overall yield. Protection with BnBr and NaH, acidic cleavage of the acetonide, olefination, acetonide formation, and addition of methallyllithium furnished derivative **7** in 45% yield. Further elaboration of fragment **7** provided cyclic key intermediate **8** which was also derived from the natural product **1** through degradation studies. The operation was completed when compound **8** was taken to an advanced intermediate, which had previously been converted into leucomycin A_3 (**1**) by Tatsuta et al.[41]

2.2. Amphotericin B and Amphoteronolide B

Amphotericin B (**9**, Scheme 10) is a clinically used antifungal agent, isolated from *Streptomyces nodosus* and, along with its aglycon, amphoteronolide B (shown in a protected form as **17**, Scheme 10), became the second synthetic target to be elaborated from carbohydrate building blocks by this group.[42–51] Retrosynthetic analysis of this complex polyene macrolide suggested that certain stereochemical and symmetry elements present in amphoteronolide B could be derived from a commercially available xylose carbohydrate. In particular, it was recognized that segments C1–C6 and



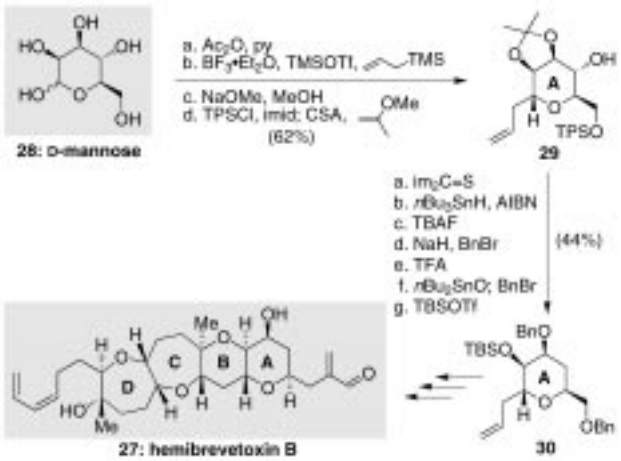
Scheme 10. Synthesis of amphoteronolide B (**17**) and amphotericin B (**9**) from D- and L-xylose (**10** and **13**, respectively) and methyl D-glucopyranoside (**24**), as well as the degradation of amphotericin B (**9**) (1987).[42–51]

C8 – C13 could be obtained from the D and L enantiomers of xylose, respectively. Thus, D-xylose (**10**) was converted into its 1,2-monoacetonide, selectively silylated at the primary position, and deoxygenated to afford intermediate **11**. Further elaboration furnished the C1 – C6 fragment **12**, whose stereochemical elements could be readily transferred to the coupled product **16** and the final target **17**. The L enantiomer of xylose (**13**) was taken through a similar sequence to afford derivative **14** and, thence, through a ten-step sequence to furnish the C8 – C13 keto phosphonate **15**. Coupling of these two intermediates **12** and **15** provided the larger C1 – C13 fragment **16** in a highly concise and efficient manner; and the latter was further elaborated to amphoteronolide derivative **17**.

Completion of the synthesis of the requisite derivative **17** enabled attention to be focused on the final drive towards amphotericin B (**9**). The difficulty of the glycosidation step was recognized from the outset of the synthesis; this difficulty was due to the inherent instability of the aglycon unit and the target molecule, the presence of a basic nitrogen on the carbohydrate moiety, and the requirement for a *β-cis*-1,2-glycoside bond. Following systematic, but unsuccessful, glycosidation studies, an indirect method for forming the correct anomeric stereochemistry was ultimately developed. Thus, as shown in Scheme 10, amphoteronolide B derivative **17** was coupled with trichloroacetimidate **18** in the presence of PPTS to afford glycoside **19**. Monosaccharide **18** (derived from methyl-D-glucopyranoside **24**) incorporated an acetate group at the C2 position with the opposite configuration to that desired in order to direct the anomeric stereochemistry. This maneuver required, however, that this center be inverted after glycosidation. This goal was easily attained by Swern oxidation and subsequent reduction with $NaBH_4$ to afford the monosaccharide with the correct stereochemistry in 80% overall yield. Further manipulations, including reduction of the azide and removal of the protecting groups, proceeded smoothly to afford the target, amphotericin B (**9**), in high overall yield. During this total synthesis, various degradation studies were performed on amphotericin B in order to remove the carbohydrate unit for spectroscopic comparison of the resulting aglycon to synthetic material, and for supplementing the amounts of advanced intermediates that were available. As such, a novel oxidative protocol for the deglycosidation of amphotericin B using NBS and $CaCO_3$ was developed for the construction of enone **21** and lactol **23**.

2.3. Hemibrevetoxin B

The brevetoxins are among the most prominent toxins associated with the "red tide" phenomenon and have been implicated in massive fish kills, mollusk poisonings, and occasional human intoxications. These molecules, produced by the dinoflagellate strain *Gymnodinium breve* DAVIS, represent a class of neurotoxins which activate sodium channels and cause repetitive firing in neurons. In a program directed towards the total synthesis of the brevetoxins, new synthetic methods were developed and applied to the total synthesis of hemibrevetoxin B,[52, 53] a molecule having a molecular size approximately half that of the brevetoxins A and B. Retrosynthetic analysis of hemibrevetoxin B (**27**, Scheme 11) revealed that the functionality present in ring A could be traced back to commercially available D-mannose (**28**), which would



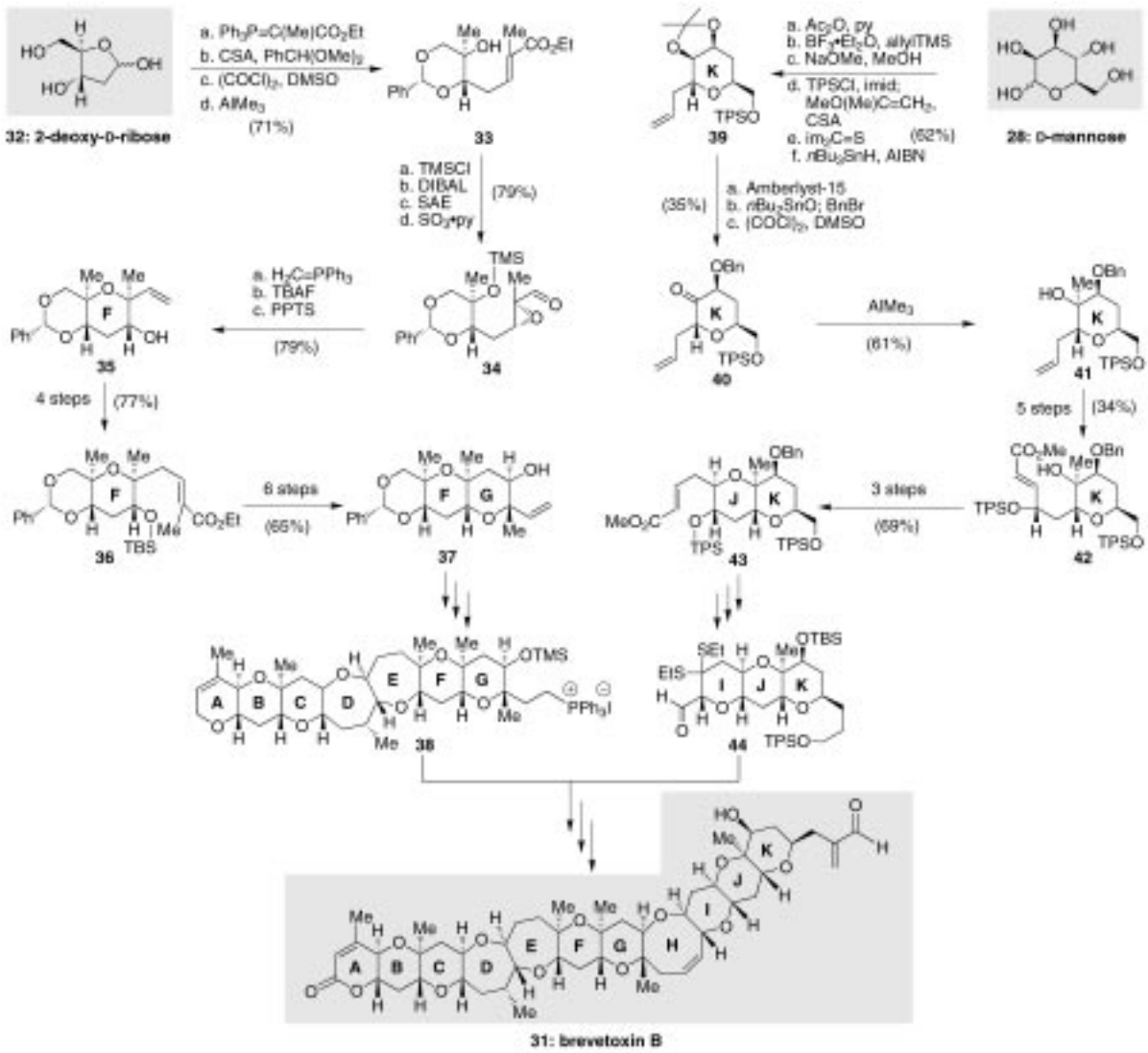
Scheme 11. Synthesis of hemibrevetoxin B (**27**) from D-mannose (**28**) (1992).[52, 53]

provide three of the ten required stereocenters. Thus, D-mannose (**28**) was peracetylated and C-glycosidated with allyltrimethylsilane in the presence of $BF_3 \cdot Et_2O$ and TMSOTf to afford a 7:1 ratio of α:β anomers. The resulting product was deacetylated, selectively silylated at the primary position, and converted into the 2,3-acetonide **29**. Further elaboration of **29** into the tetrahydropyran systems in a linear fashion was achieved through regio- and stereoselective epoxide-opening/ring-closing procedures, culminating in the total synthesis of hemibrevetoxin B (**27**) in 1992, the first member of the brevetoxin class to be synthesized in the laboratory.

2.4. Brevetoxin B

Brevetoxin B (**31**, Scheme 12) was the first member of this class of marine natural products to be structurally elucidated and is also one of the most potent. It has a novel polycyclic framework consisting of 11 rings (eight 6-membered, two 7-membered, and one 8-membered) fused together by *trans* junctions with 23 stereocenters. Carbohydrates seemed excellent precursors to the tetrahydropyran rings found in brevetoxins in that several of the stereocenters could be established concurrently, particularly those centers flanking the oxygens. The number of carbohydrate units to be incorporated depended upon the successful coupling of advanced intermediates in either a convergent, or sometimes, linear fashion. During the initial studies directed towards the development of novel synthetic methods and the investigation of coupling strategies, carbohydrates were used to prepare many of the model systems and several of the tetrahydropyran rings. In the final and successful linear approach to brevetoxin B,[54–67] two of the tetrahydropyran motifs, rings F and K, were derived from carbohydrates.

As shown in Scheme 12, 2-deoxy-D-ribose (**32**) was utilized as a starting material for the F ring tetrahydropyran. Thus,

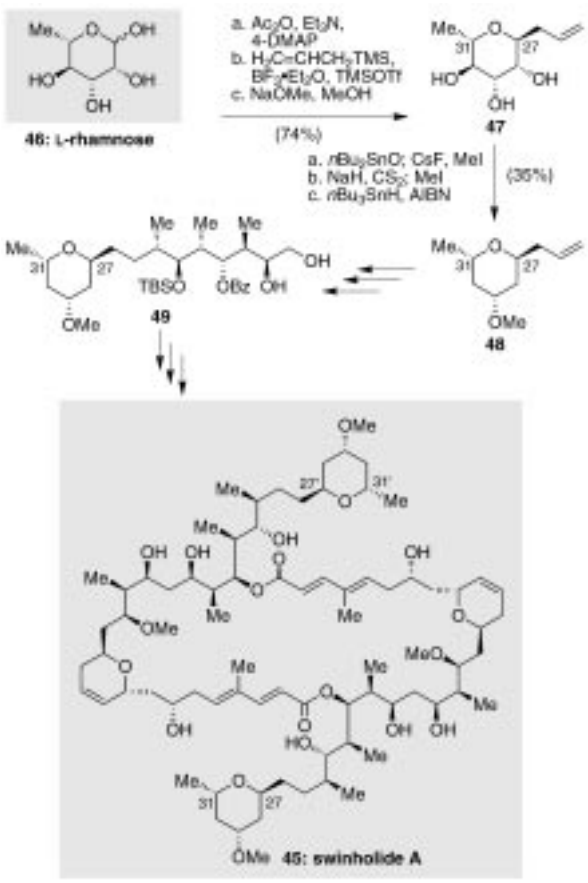


Scheme 12. Synthesis of brevetoxin B (**31**) from 2-deoxy-D-ribose (**32**) and D-mannose (**28**) (1995).[54–67]

treatment of **32** with (carbethoxyethylidene)triphenylphosphorane was followed by formation of the thermodynamically favored benzylidene acetal, Swern oxidation of the remaining alcohol, and exposure of the resulting carbonyl compound to $AlMe_3$ to introduce the methyl group. Completion of ring F involved silylation of the tertiary alcohol, DIBAL reduction, Sharpless asymmetric epoxidation, $SO_3 \cdot py$ oxidation, olefination, and PPTS-catalyzed epoxide-opening/cyclization to afford tetrahydropyran derivative **35** in 44% overall yield. Further elaboration of the "right-hand" side of ring F furnished FG segment **37** via **36** in 50% yield for ten steps; this segment was ultimately incorporated into the target, brevetoxin B (**31**). Scheme 12 also illustrates the conversion of D-mannose (**28**) into ring K derivative **39**, followed by completion of this ring system by removal of the acetonide with Amberlyst-15, tin acetal mediated monobenzylation, Swern oxidation, and addition of $AlMe_3$ to afford tertiary alcohol **41** in 13% overall yield. Elaboration of the "left-hand" side of ring J furnished JK segment **43** in 23% yield for eight steps; this segment was again incorporated into the final target, brevetoxin B (**31**), in its total synthesis in 1995.

2.5. Swinholide A

Swinholide A (**45**, Scheme 13), a marine natural product isolated from the sponge *Theonella swinhoei*, displays impressive biological properties, including antifungal activity and potent cytotoxicity against a number of tumor cell lines. The molecular structure of swinholide A (**45**) is distinguished by a C_2-symmetric 44-membered macrolide ring, two conjugated diene systems, two trisubstituted pyran systems, two disubstituted dihydropyran systems, and a total of 30 stereocenters. Retrosynthetic analysis of this complex macrolide revealed that the C27–C32 segment could be obtained from commercially available L-rhamnose (**46**), which would provide the correct stereochemistry for the C27, C29, and C31 centers of this pyran moiety.[68–71] Thus, peracetylation of L-rhamnose (**46**) followed by C-glycosidation with allyl trimethylsilane in the presence of TMSOTf and $BF_3 \cdot Et_2O$ and subsequent deacetylation afforded, exclusively, the desired α-glycoside **47**. Regioselective tin acetal mediated protection as a methyl ether at the C3 position was followed by Barton–McCombie deoxygenation of the remaining two alcohols to



Scheme 13. Synthesis of swinholide A (**45**) from L-rhamnose (**46**) (1995).[68–71]

afford olefin **48**. Further elaboration of the C27 – C32 segment allowed for its eventual incorporation into swinholide A (**45**).

2.6. Brevetoxin A

Brevetoxin A (**50**, Scheme 14) is the most potent neurotoxin in the brevetoxin family. Its synthetic challenge originates from the high complexity of its molecular structure consisting of 10 rings, which contain 5 – 9 members, inclusively, surrounded by 22 stereocenters. Retrosynthetically, D-glucose was recognized as a potential central scaffold for ring C to allow for the installation of the four stereocenters situated on this ring; the 8- and 7-membered rings (B and D) could be elaborated around this. As with the other brevetoxins, D-mannose was envisioned to provide three stereocenters present in the "right-hand" region of the molecule, encompassing the ring J tetrahydropyran moiety and allowing for facile extension of the necessary side chain. Thus, D-glucose (**3**, Scheme 14) was transformed into its 1,2;5,6-bisacetonide and deoxygenated at position C3. Selective cleavage of the 5,6-acetonide with H_5IO_6 furnished aldehyde **51**. Sequential addition of MeMgBr and Swern oxidation led to the methylketone. Reaction of the latter compound with allylmagnesium bromide in the presence of $Ti(iPrO)_4$ led, stereoselectively, to the tertiary alcohol and was followed by cleavage of the acetonide with $EtSH/ZnCl_2$, dibenzylation, I_2-mediated hemiacetal formation, olefination, and finally, CSA-catalyzed ring closure to furnish ring C derivative **53** in 34% overall yield from **51**. Further elaboration of **53** led successively to **54** and **55**. D-Mannose (**28**) was processed in a similar fashion to that described in Schemes 11 and 12, to furnish the ring J derivative **56** in 27% yield over nine steps (Scheme 14). Further elaboration of the latter intermediate led to the IJ segment **58** and thence to **59**. The segments **55** and **59** were then coupled and elaborated to brevetoxin A (**50**) through the dithioketal cyclization strategy.[72–79]

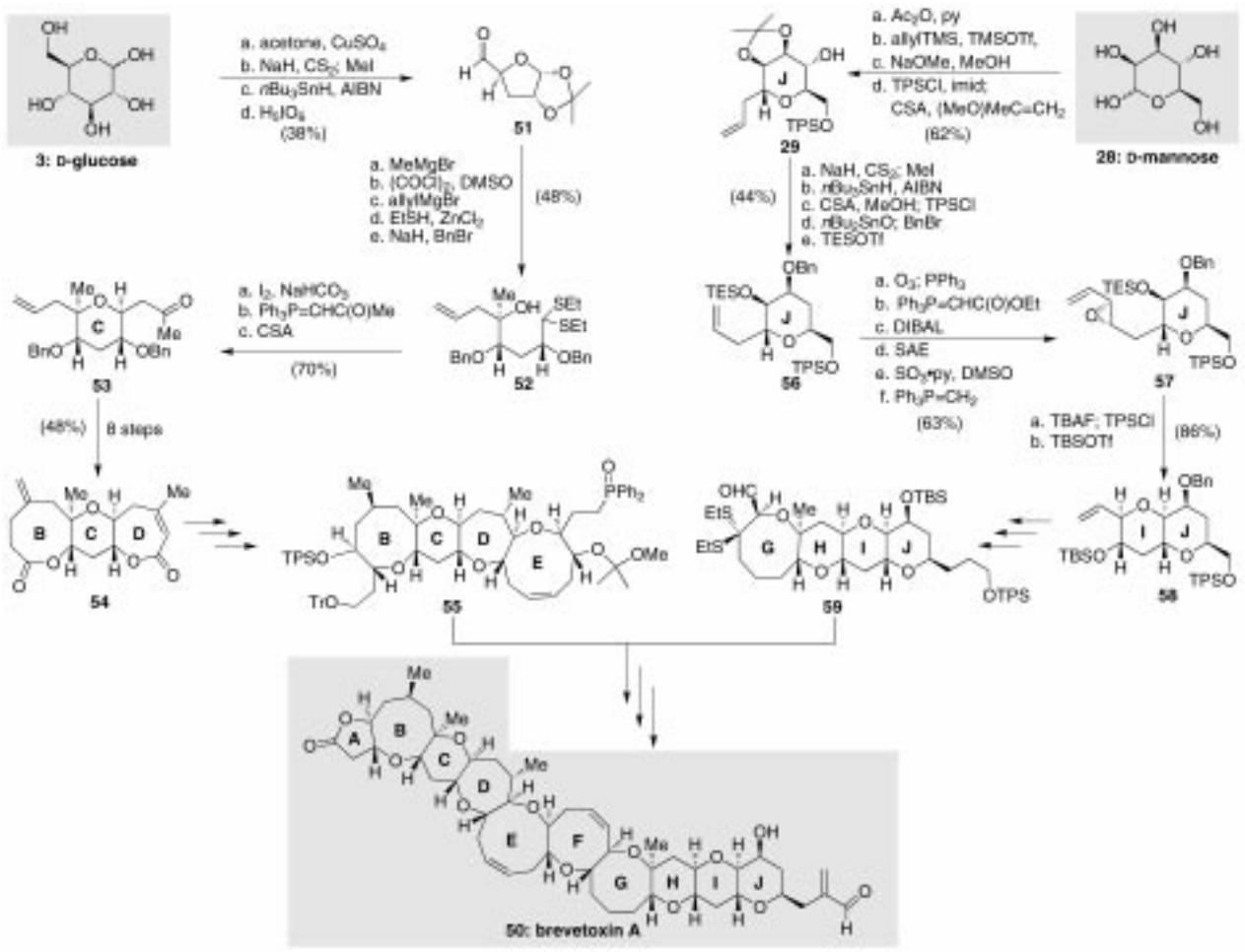
Before extending the discussion to encompass the total synthesis of complex oligosaccharide-containing natural products, it will be instructive to present a number of new methods and technologies developed en route to these natural products.

3. New Synthetic Technologies in Carbohydrate Chemistry

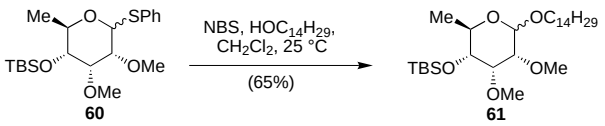
Over the years our excursions into the realm of carbohydrate chemistry brought us face-to-face with a myriad of challenges and provided us opportunities to discover and invent novel synthetic technologies and strategies, both for the construction of carbohydrate templates and their utilization in organic synthesis. Such methods and processes included the synthesis of activated glycosyl donors, new glycosidation procedures, new methods for C-glycosidations, new methods for the formation of 2-deoxyglycosides, 1,1′-disaccharides, and orthoesters, new strategies for solid-phase synthesis of oligosaccharides, and new processes for the construction of aminosugars and their derivatives. Below we will discuss, in chronological order, these developments and place them in perspective within the larger domain of organic synthesis.

Noting the ready availability, relative stability, and potential of thioglycosides as glycosyl donors,[80] we searched for a non-metal based activation procedure for these intermediates (in contrast to Ferrier et al.'s original use of mercuric salts for activation[16a]). In 1983 we reported a mild method for the synthesis of *O*-glycosides from phenylthioglycosides with NBS as an activator.[16b] This procedure, which was preceeded by a report from the Hanessian laboratories[16f] in which NBS was utilized to activate a 2-pyridylthioglycoside to form α- and β-methyl glycosides (by solvolysis in methanol/acetonitrile (1/1) under reflux), was found to be quite general and simple to employ as demonstrated by the many substrates shown to enter the reaction. Scheme 15 shows the reaction in which phenylthioglycoside **60** was converted into *O*-glycoside **61** ($\alpha:\beta \approx 5:1$) in 65% yield upon treatment with the required straight chain alcohol in the presence of NBS in CH_2Cl_2 at 25 °C. Selected examples of this reaction are provided in Table 1.

Our 1983 publication[16b] reporting the first practical thioglycoside-based glycosiation method with an electrophilic reagent (that is, NBS) was followed by a number of other useful modifications such as the use of DMTST (for example,

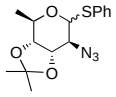
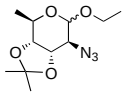
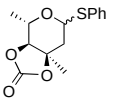
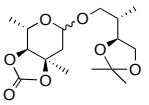
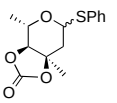
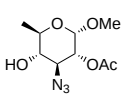
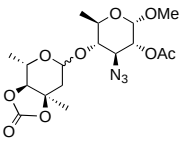
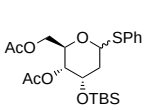
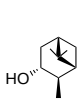
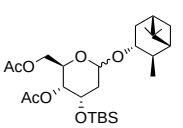


Scheme 14. Synthesis of brevetoxin A (**50**) from D-mannose (**28**) and D-glucose (**3**) (1998).[72–79]



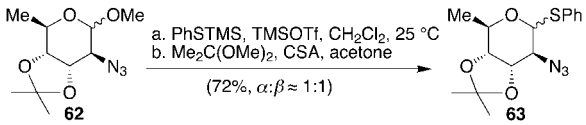
Scheme 15. NBS-promoted synthesis of O-glycosides (such as **61**) from phenylthioglycosides (like **60**) (1983).[16b, 80]

Table 1. Selected examples of NBS-promoted synthesis of O-glycosides from phenylthioglycosides.[16b, 80]

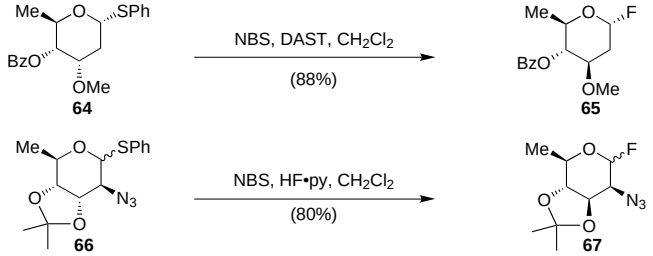
Phenylthio-glycoside	Alcohol	O-Glycoside	Solvent	Yield [%]	α:β
			CH_2Cl_2	78	1:1
			MeCN	75	3:1
			MeCN CH_2Cl_2	72 72	1:1 9:1
			CH_2Cl_2	82	2:1

by Garegg and co-workers in 1986[16c]), IDCP (for example, by van Boom and co-workers in 1990[16d]), and NIS/TfOH (for example, by van Boom and co-workers in 1990[16e]). In addition, during the course of these studies a new method for the direct conversion of methyl glycosides into phenylthioglycosides was developed.[9] As shown in Scheme 16, this procedure involves exposure of the methyl glycoside (such as **62**) to PhSTMS and TMSOTf in CH_2Cl_2 at 25 °C.

In an effort to develop a streamlined process for the synthesis of oligosaccharides, we undertook an exploration into the chemistry of glycosyl fluorides. Thus, merging the excellent glycosidation properties of glycosyl fluorides, previously reported by Mukaiyama et al.,[7] with the newly discovered ability of phenylthioglycosides to afford glycosyl fluorides upon exposure to NBS/DAST or NBS/HF·py (**64**→**65** and **66**→**67**, Scheme 17 and Table 2), we developed the "two-stage activation" procedure for the synthesis of complex oligosaccharides.[9] This reiterative procedure combines the differential and orthogonal reactivities of glycosyl fluorides, phenylthioglycosides, and silyl ethers to achieve a reliable sequence for oligosaccharide chain growth (Scheme 18). Thus, clean conversion of a monosaccharide

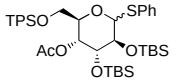
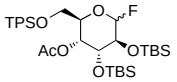
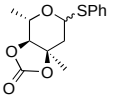
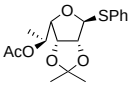
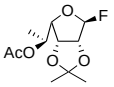
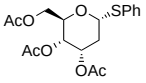
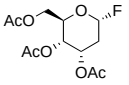


Scheme 16. Synthesis of phenylthioglycosides (such as **63**) from methyl glycosides (like **62**) (1982).[9]

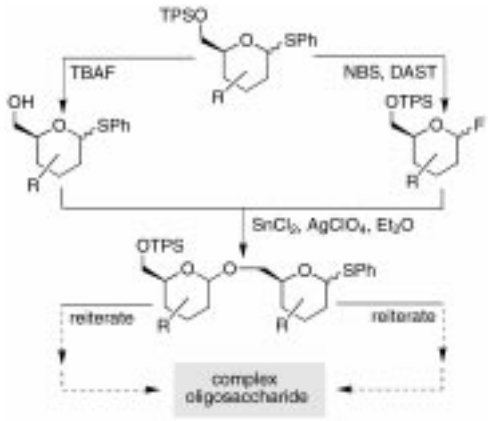


Scheme 17. Formation of glycosyl fluorides from phenylthioglycosides (1984).[9]

Table 2. Selected examples of glycosyl fluoride formation from phenylthioglycosides.[a][9]

Phenylthioglycoside	Glycosylfluoride	Method	Yield [%]	$\alpha:\beta$
		A B	82 74	5:1 5:1
		A	75	1:2
		A B	91 80	
		A	70	

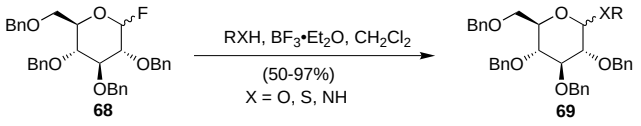
[a] Method A: DAST/NBS; Method B: NBS/HF · py.



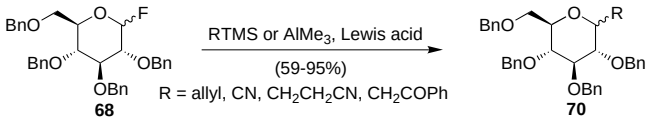
Scheme 18. Practical, reiterative synthesis of oligosaccharides by the two-stage activation procedure (1984).[9]

unit containing a phenylthio group at C1 and a relatively robust silyl ether group (such as TPS) at C6 to the corresponding glycosyl fluoride (NBS/DAST) and the primary alcohol (TBAF), respectively, is followed by coupling with $SnCl_2/AgClO_4$ to furnish a disaccharide equipped with both a phenylthio and a silyl group. Reiteration of the process then leads to a new pair of disaccharide donor and acceptor, from which a tetrasaccharide may be formed and so on. Several applications of this technology in complex oligosaccharide synthesis have been demonstrated; some of these syntheses will be discussed below.

Further explorations of the chemistry of glycosyl fluorides led to efficient methods for the O-, N-, S-,[11] and C-glycosidations[81] (Schemes 19 and 20, and Tables 3 and 4). A search



Scheme 19. Synthesis of N-, O-, and S-glycosides from glycosyl fluorides (1984).[11]



Scheme 20. Synthesis of C-glycosides from glycosyl fluorides (1984).[81]

Table 3. Selected examples of the synthesis of N-, O-, and S-glycosides from glycosyl fluoride **68**.[11]

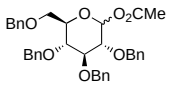
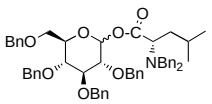
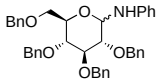
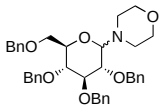
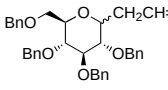
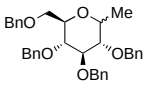
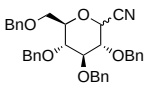
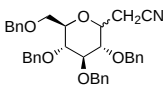
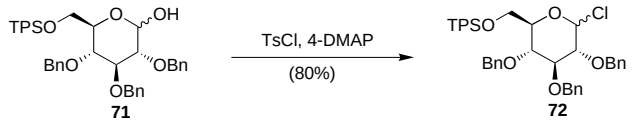
Reagents, temperature	Products	Yield [%]	$\alpha:\beta$
$MeCO_2H$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C		97	3:2
$Me_2CHCH_2CH(NBn_2)CO_2H$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C		76	10:1
$PhNH_2$, $AlMe_3$, CH_2Cl_2, 25 °C		65	1:1
morpholine, $MgBr_2 \cdot Et_2O$, CH_2Cl_2, 25 °C		90	1:10

Table 4. Selected examples of the synthesis of C-glycosides from glycosyl fluoride **68**.[81]

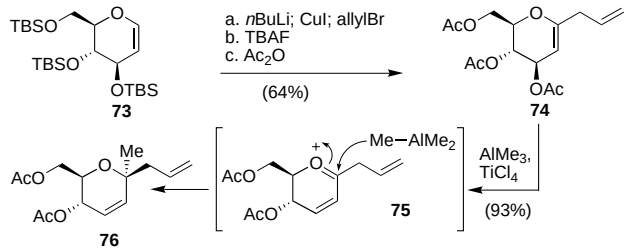
Reagents	Product	Yield [%]	$\alpha:\beta$
allylTMS, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C		95	> 20:1
$AlMe_3$, toluene, 0 °C		95	> 20:1
$AlMe_2CN$, toluene, 0 °C		96	10:1
$TMSCH_2CN$, $BF_3 \cdot Et_2O$, CH_2Cl_2, 25 °C		85	3:1

for new reactions forming glycosyl halides led to a new method for forming glycosyl chlorides from lactols and tosyl chloride in the presence of 4-DMAP (Scheme 21).[82] In



Scheme 21. Formation of glycosyl chlorides (such as **72**) from lactols (like **71**) (1984).[82]

connection with our program directed towards the total synthesis of brevetoxin B (**31**), we developed a general and stereospecific synthesis of 1,1-dialkyl glycosides. Reported in 1986[83] and depicted in Scheme 22, this method is exemplified

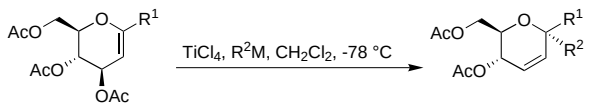


Scheme 22. Stereoselective synthesis of 1,1-dialkylglycosides (such as **76**) from glycals (like **73**) (1986).[83]

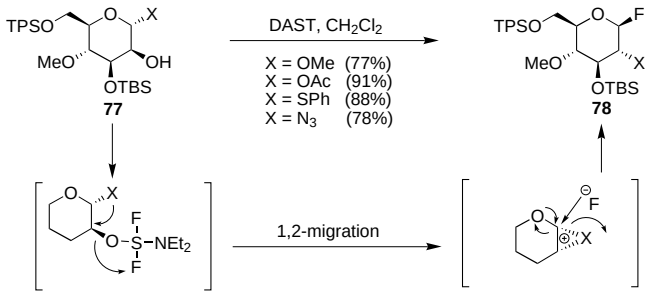
by the synthesis of derivative **76** from glycal **73**. Thus, processing of trisilylether **73** through a modified Boeckman procedure followed by exchange of protecting groups furnished 1-allylated glycal **74** in 64% overall yield. Further alkylation of **74** with $AlMe_3/TiCl_4$ furnished stereospecifically, and through the indicated intermediate **75**, the 1,1-dialkylated compound **76** in high overall yield. Additional examples are illustrated in Table 5.

During our continuing explorations in the areas of functionalization of ring systems and the stereocontrolled construction of glycoside bonds, a new series of stereospecific 1,2-migrations within the pyranoside framework was discovered.[84, 85] As illustrated in Scheme 23, treatment of 2-hydroxy carbohydrate frameworks, with various substituents at the C1 position, with excess DAST in CH_2Cl_2 at 0–45 °C led to

Table 5. Selected examples of 1,1-dialkylglycosides.[83]

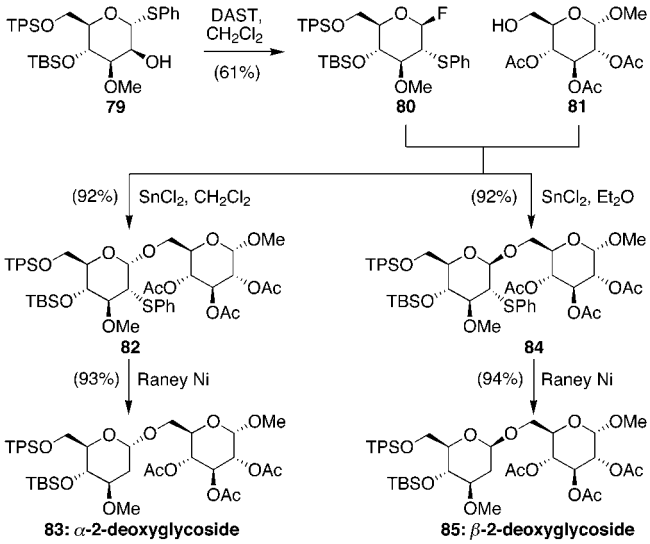


Reagent (R^2M)	Product		Yield [%]
	R^1	R^2	
$AlMe_3$	Me	Me	92
$AlEt_3$	Me	Et	82
TMSCN	Me	CN	82
TMSC≡CMe	Me	C≡CMe	79
allylTMS	Me	$CH_2CH{=}CH_2$	75
Et_3SiH	$CH_2CH{=}CH_2$	H	92
$AlMe_3$	$CH_2CH{=}CH_2$	Me	83



Scheme 23. DAST-promoted 1,2-migrations in carbohydrates (1986).[84]

smooth 1,2-migration of the anomeric substituent with simultaneous installation of a fluoride at C1. Anomeric substituents capable of this migration include methoxy, acetoxy, phenylthio, azide, benzyloxy, and sugar oxy groups, and they all afford the glycosyl fluorides in high yield. Thus, in one step, this operation introduces a variety of useful functional groups at the C2 position and also a fluorine substituent at C1 with inversion of configuration at both centers. These facile migrations found a number of useful applications. To name a few, the resultant glycosyl fluorides can be employed in coupling reactions with nucleophiles to afford O-, N-, S-, and C-glycosides. Use of a group capable of rupture leads to inversion of the C2 stereochemistry, whereas reductive removal of a C2 thiophenyl group leads to 2-deoxyglycosides. The latter approach is illustrated in Scheme 24. As shown,

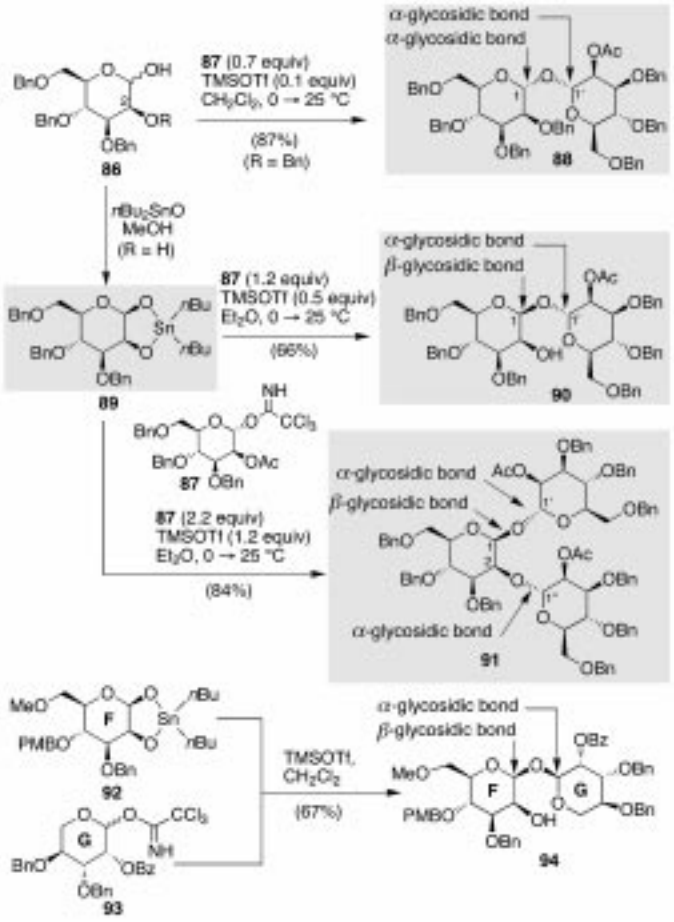


Scheme 24. Stereocontrolled synthesis of α- and β-2-deoxyglycosides from 2-hydroxy-phenylthioglycosides (1986).[84]

DAST-promoted migration of thioglycoside **79** furnished glycosyl fluoride **80**, which underwent smooth coupling with an alcohol such as **81** in Et_2O and in the presence of $SnCl_2/AgClO_4$ to afford the disaccharide **84**. Desulfurization of **84** by Raney nickel resulted in the formation of the 2-deoxy-β-disaccharide **85**. Significantly, utilization of CH_2Cl_2 as the solvent for the coupling step, followed by desulfurization, opens entry into the 2-deoxy-α-disaccharide series of compounds such as **83**. Thus, application of this technology affords

selectively, and at will, the α- and β-glycosides with high stereocontrol.

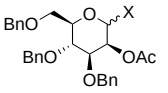
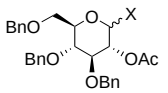
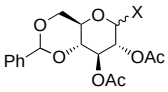
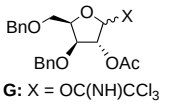
More recently (1997), during our program directed towards the total synthesis of the everninomicin oligosaccharide antibiotics, a new technology for the construction of 1,1′-disaccharides and 1,1′;1″,2-trisaccharides was developed (Scheme 25).[86] Among the challenging features of the everninomicin antibiotics is the 1,1′-bridge linking rings F and G in



Scheme 25. Stereoselective construction of 1,1′-disaccharides and 1,1′;1″,2-trisaccharides by tin acetal technology (1997).[86]

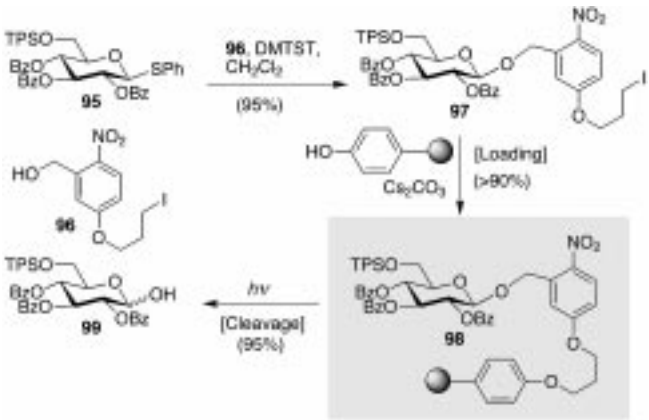
a β-mannoside fashion (see structure of everninomicin 13,384-1 (**344**), Scheme 58). Construction of a linkage of this type requires control of the stereochemistry at both anomeric centers while forming the new bond. For example, treatment of a lactol such as **86** with an activated donor **87** in the presence of TMSOTf furnished the undesired disaccharide **88** containing the 1α,1′α-stereochemistry. However, fixation of the anomeric configuration of **86** by conversion into the 5-membered ring stannane **89** and subsequent treatment with trichloroacetimidate **87** in the presence of TMSOTf delivered the desired 1β,1′α-disaccharide **90**. Other selected examples of di- and trisaccharide formation are shown in Table 6. Furthermore, exposure of stannane **89** to 2.2 equivalents of trichloroacetimidate **87** in the presence of TMSOTf furnished the 1,1′:1″,2-trisaccharide **91**, in which all three glycosidic linkages were formed stereoselectively. This technology was

Table 6. Selected examples of β-linked 1,1′-disaccharides and 1,1′;1″,2-trisaccharides (see Scheme 25).[86]

Equiv **89**	Donor		t [h]	Disaccharide yield [%]	Trisaccharide yield [%]
1.5		**A**	35	66	9
0.45		**A**	72	–	–
1.5		**B**	24	10	70
0.45	**A:** X = $OC(NH)CCl_3$ **B:** X = F	**B**	24	–	84
1.5		**C**	48	68	–
0.45		**C**	96	22	47
1.5		**D**	48	64	–
0.45	**C:** X = $OC(NH)CCl_3$ **D:** X = F	**D**	72	23	32
1.5		**E**	72	57	22
0.45		**E**	72	58	14
1.5		**F**	0.5	59	5
0.45	**E:** X = $OC(NH)CCl_3$ **F:** X = F	**F**	48	–	33
1.5		**G**	0.5	72	8
1.5		**G**	0.5	70	12
	G: X = $OC(NH)CCl_3$				

further applied to the FG model system also depicted in Scheme 25. Thus, coupling of stannane **92** and trichloroacetimidate **93** in the presence of TMSOTf furnished the desired disaccharide **94** in 67% yield. This method was eventually applied to the real system and was a necessary step in facilitating the total synthesis of everninomicin 13,384-1 (described in Section 4.18).

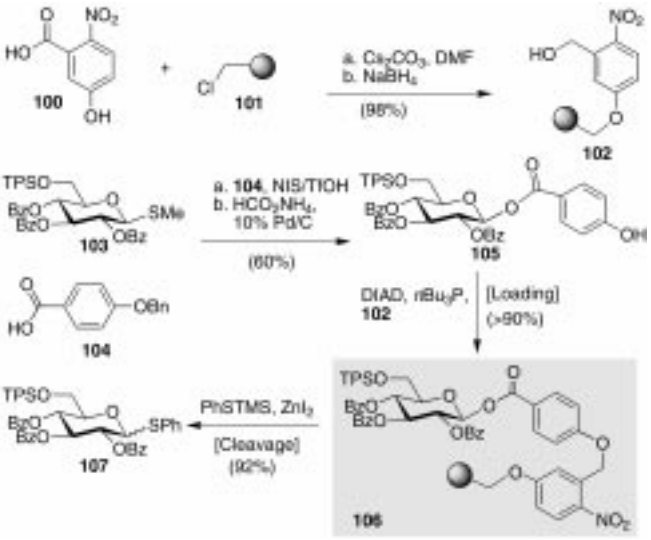
With the emergence of combinatorial chemistry as a powerful tool in the drug discovery process, solid-phase chemistry has assumed a central position in organic synthesis. In this light, the design of new linkers and strategies for the solid-phase synthesis of oligosaccharides was deemed important. Scheme 26 illustrates the synthesis and application of a first generation photolabile linker to the solid-phase synthesis of oligosaccharides, reported from these laboratories in 1997.[87] Thus, glycosidation of 2-nitrobenzyl alcohol **96** with phenylthioglycoside **95** in the presence of DMTST afforded the β-glycoside **97**. Monosaccharide **97** was then attached to



Scheme 26. Synthesis and utilization of a photolabile linker for oligosaccharide synthesis (1997).[87]

the phenolic polystyrene resin through its linker to afford conjugate **98**. Efficient cleavage of the carbohydrate fragment from the resin was demonstrated by irradiation in THF at 25 °C, whereby the monosaccharide **99** was afforded in 95 % yield. This linking strategy was ultimately applied to the synthesis of the complex oligosaccharide HPE, as will be described in Section 4.14.

Despite its efficiency, the above method suffered from anomeric mixtures at every cleavage step and it was necessary to reactivate the cleavage product prior to possible reincorporation into the growing oligosaccharide chain. Thus, a new procedure which dealt with both of these issues by incorporating a spacer between the photolabile linker and the anomeric position of the first glycoside was developed and reported in 1998.[88] Illustrated in Scheme 27, this new strategy



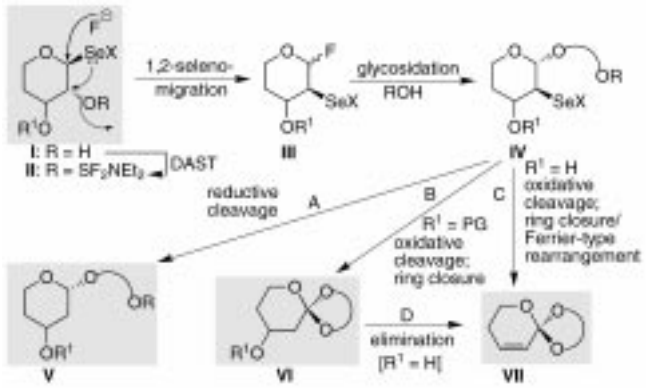
Scheme 27. Second generation strategy towards the solid-phase synthesis of oligosaccharides (1998).[88]

appeared ideal for the block-type construction of large and diverse oligosaccharides. Thus, β-phenolic ester **105** was easily obtained from thioglycoside **103** by reaction with **104** in the presence of NIS/TfOH, followed by removal of the benzyl group to furnish **105** in 60 % overall yield. Attachment of the phenolic monosaccharide **105** to the solid support **102** was then achieved under Mitsunobu conditions to furnish conjugate **106**. Cleavage of the monosaccharide from the resin was facilitated by treatment with PhSTMS/ZnI_2 to afford thioglycoside **107**, which was directly ready for coupling as the next block. The efficiency of this procedure was demonstrated by the synthesis of a dodecasaccharide, as will be described in Section 5.3.

Also in 1998, the exploration of polymer-supported selenium reagents for organic synthesis led us to the synthesis of polymer-bound selenium bromide and selenium phthalimide reagents applicable to the synthesis of 2-deoxyglycosides (Scheme 28).[89] Reaction of tribenzyl glucal **108** with the polymer-bound selenenyl bromide and alcohol **109**, followed by reductive cleavage of the newly formed selenium–carbon bond by treatment with nBu$_3$SnH/AIBN released the 2-deoxyglycoside **110** with an α:β ratio of approximately 8:1. Alternatively, treatment of a mixture of the same glucal (**108**) and alcohol (**109**) with the polymer-bound selenenyl phthalimide reagent followed by radical cleavage led to disaccharide **110** as an approximately 1:1 mixture of α:β anomers.

Scheme 28. Application of organoselenium resins in the synthesis of 2-deoxyglycosides (1998).[89]

During the total synthesis of everninomicin and recalling the 1,2-thiophenyl migrations on carbohydrate templates and the newly developed polymer-bound selenium bromide resin, a general concept for the solid- and solution-phase syntheses of 2-deoxyglycosides, orthoesters, and allylic orthoesters through 1,2-selenium migrations was proposed (Scheme 29).[90] Thus, treatment of the readily available



Scheme 29. General concept for the stereoselective solid-phase synthesis of 2-deoxyglycosides **V**, orthoesters **VI**, and allylic orthoesters **VII** through 1,2-selenium migrations (2000). X = Ph or polystyrene.[90]

2-hydroxy-1-selenoglycoside **I** with DAST resulted in a stereospecific 1,2-migration of the selenium moiety, with simultaneous installation of a fluoride group at C1 to furnish **III**. The desired α-glycosides **IV** resulting from participation of the seleno group, were formed upon exposure of these reactive donors **III** to various hydroxy components in the presence of Lewis acids. From **IV**, one of the following three paths could be followed:

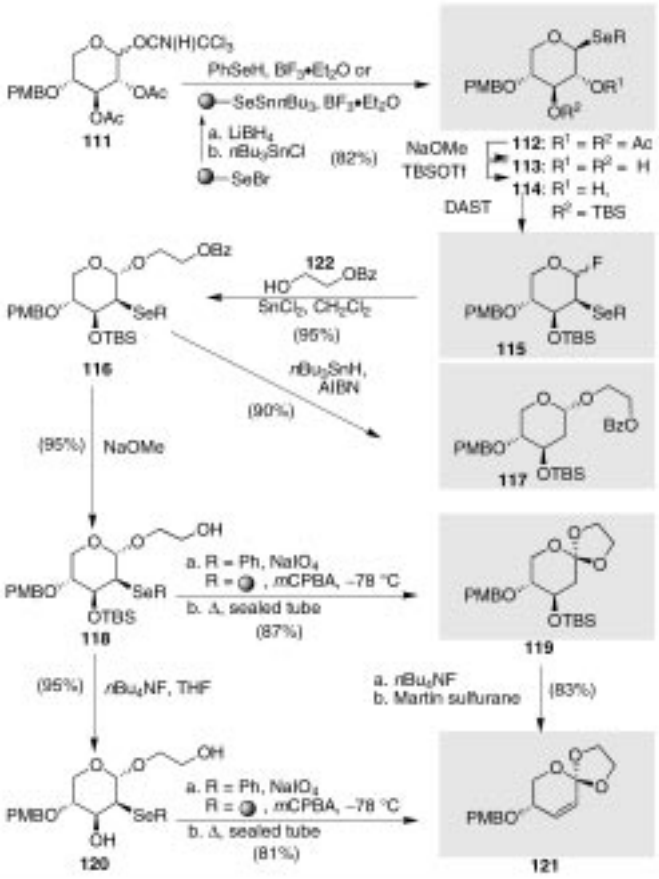
Path A: Radical deselenation facilitated by nBu$_3$SnH and furnishing the 2-deoxyglycosides **V**,

Path B: 2-Deoxyorthoesters **VI** could be obtained, which would require initial removal of the protecting group R and then oxidation of the selenium to the selenoxide and heating to promote the required *syn*-elimination and concomitant cyclization,

Path C: Both protecting groups (R and R^1) would be removed before subsequent oxidation and heating,

to afford the 2,3-allylic orthoesters (**VII**) through a Ferrier-type rearrangement. Furthermore, elimination of the hydroxy group of **VI** would again furnish **VII** (path D), which would allow the scope of the process to be expanded and comparisons to be made of the stereochemistries of the orthoester moieties generated from paths B and C.

Scheme 30 exemplifies the chemistry, both in solution (R = Ph) and on solid phase (R = ● = polystyrene) for the synthesis of 2-deoxyglycoside **117** and orthoesters **119** and **121**. Thus, treatment of **114** with DAST facilitated the 1,2-phenylseleno



Scheme 30. Synthesis of 2-deoxyglycosides and orthoesters through 1,2-phenylseleno migrations (2000).[90]

migration affording the 2-phenylseleno-1-fluoro donor **115**. This operation was followed by coupling with alcohol **122** in the presence of $SnCl_2$ in CH_2Cl_2, which lead to the selective formation of α-glycoside **116**. Exposure of **116** to nBu$_3$SnH/AIBN furnished 2-deoxyglycoside **117** through radical cleavage of the C–Se bond. Removal of the benzoate group from **116**, followed by oxidation of the selenium moiety to the selenoxide and subsequent heating led to the formation of 2-deoxyorthoester **119** in 87% yield. On the other hand, removal of the silyl group from **118** followed by oxidation to the corresponding selenoxide and heating in a sealed tube as described above, furnished the 2,3-allylic orthoester **121** in 81% yield, through *syn*-elimination, ring closure, and expulsion of the C3 hydroxyl group. Orthoester **119** was converted into allylic orthoester **121** by deprotection and elimination, a procedure that was found useful in the stereochemical assignment of more complex orthoesters.

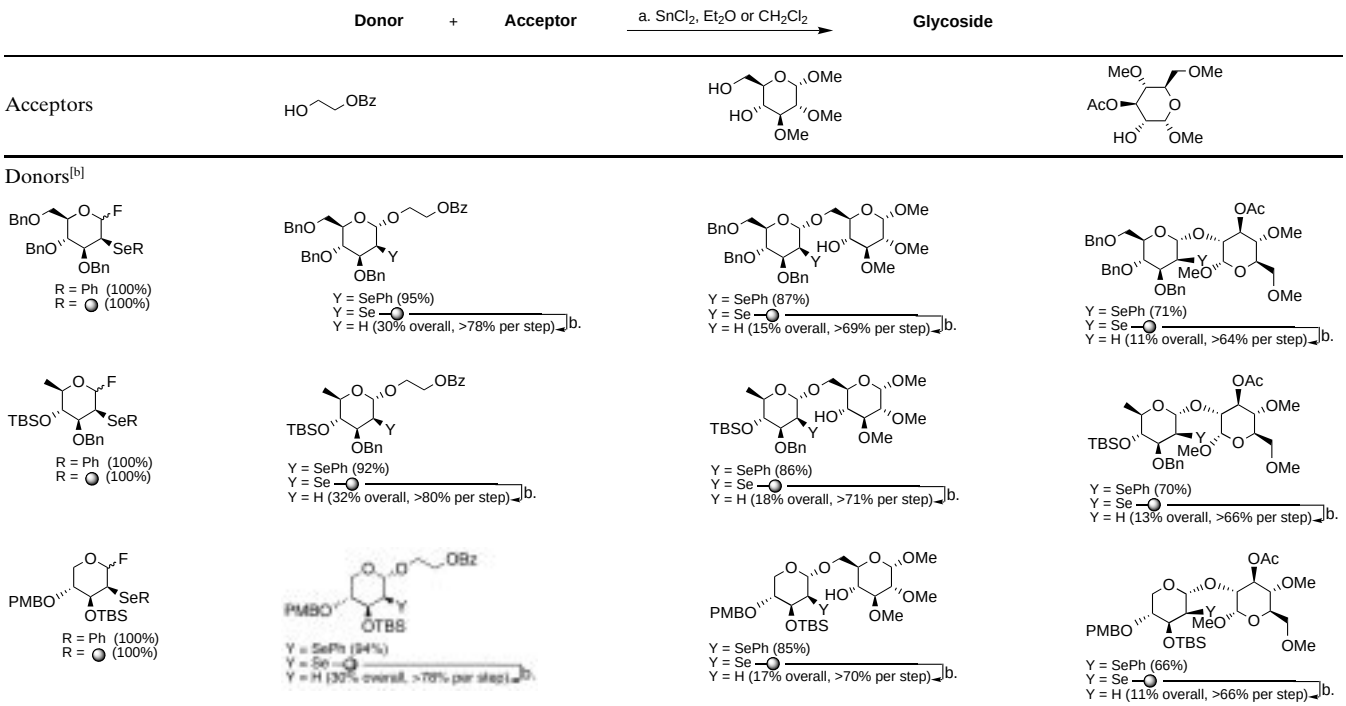
The solid-phase version of this chemistry required a suitable resin-bound selenol that could be manipulated in air. Towards this end, the previously reported polystyrene selenium bromide resin (●-SeBr)[89] was lithiated ($LiBH_4$, THF) and the resulting lithioselenide resin (●-SeLi) was quenched with excess nBu$_3$SnCl to furnish a colorless, odorless resin (●-SeSnnBu$_3$); this resin could be quickly filtered in air and immediately used in coupling reactions. Subsequent treatment of a coupled selenide resin (such as **118**, R = ●) with *m*CPBA in CH_2Cl_2 at $-78\,^{\circ}C$, followed by rapid filtration, transfer to a sealed tube, and heating furnished orthoester **119** in 78% yield. Diol **120** (R = ●) yielded **121** on similar treatment as expected. The generality and scope of the solid-phase synthesis of 2-deoxysugars, orthoesters, and 2,3-allylic orthoesters have been examined and have proven to be quite extensive (Tables 7 and 8).

One of the most recent developments in our laboratories involves the novel IBX-mediated introduction of an *N*-aryl amino functionality onto allylic alcohols (Scheme 31).[91] Examples of this IBX-mediated construction of amino sugars are shown in Scheme 32. Furthermore, the method was successfully applied to the synthesis of vancosamine (**133**; Scheme 33). Thus, intermolecular Kishi–Nozaki coupling of vinyl iodide **129** with **130** led to a 1:1 mixture of alcohols which were oxidized (DMP) and reduced under Luche conditions to afford the desired isomer. Condensation of the resulting alcohol with *p*-methoxyphenyl isocyanate in the presence of DBU followed by global deprotection (HF·py), selective primary alcohol oxidation (IBX), and protection of the anomeric hydroxy group (PMBOH, HCl(g)) furnished the cyclization precursor **132**. IBX-controlled cyclization, CAN-mediated deprotection, and basic hydrolysis completed this rapid and stereocontrolled synthesis of the targeted amino sugar, **133**.

4. Total and Partial Synthesis of Natural Products Containing Mono- and Oligosaccharides

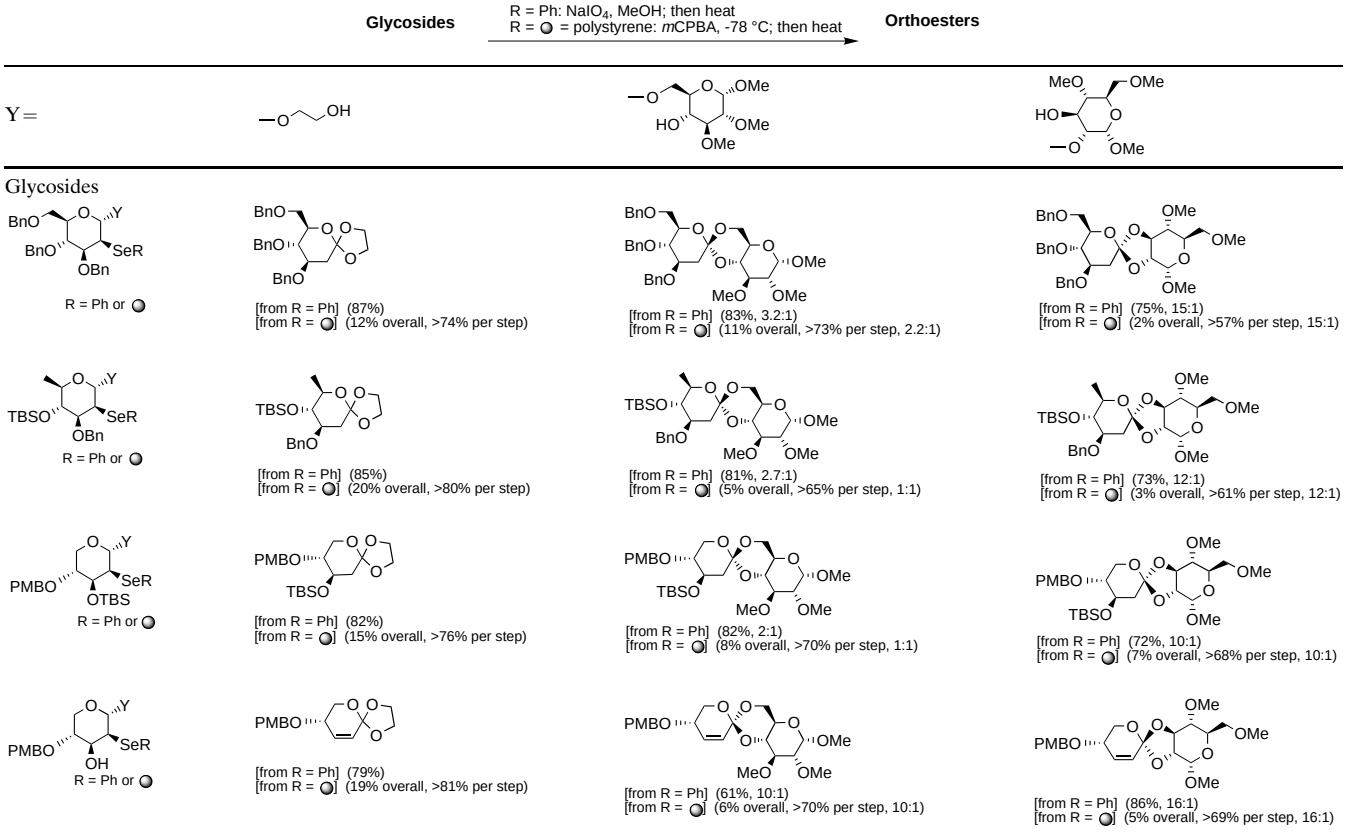
Before embarking on ambitious schemes for the total and partial synthesis of complex oligosaccharides and carbohydrate-containing natural products, several issues require careful consideration. The first such issue to be decided is the precise moment of the carbohydrate attachment within the planned sequence so as to optimize efficiency and compatibility of functionalities in subsequent steps. The second issue pertains to the choice of glycosidation method to be employed. Compatibility is often required between large fragments, individual monosaccharides and various protecting groups. The third, and sometimes most challenging issue, has to do with the choice of protecting group ensembles, with the details ranging from the development of an overall strategy to subtle, but frequently necessary, interconversions. While such problems were discussed in detail in the full accounts of each synthesis, herein only the highlights of the overall strategies and rationales leading to these successful total and partial syntheses are presented.

Table 7. Solution- and solid-phase synthesis of 2-phenylselenoglycosides and 2-deoxyglycosides (see Scheme 30).[a][90]

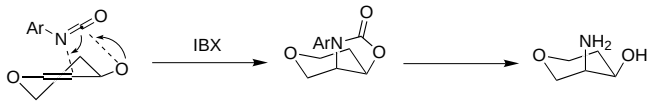


[a] Synthesis of glycosides: a) R = Ph: acceptor (1.5 equiv), $SnCl_2$ (1.5 equiv), Et_2O, 0 °C, 3 h; R = polystyrene: acceptor (10.0 equiv), $SnCl_2$ (3.0 equiv), CH_2Cl_2, 0 °C, 3 h; b) nBu$_3$SnH, AIBN, benzene, 80 °C, 1 h; ● = polystyrene. [b] Donors were prepared by DAST-induced 1,2-migration from the corresponding 2-hydroxy-β-phenylselenoglycosides.

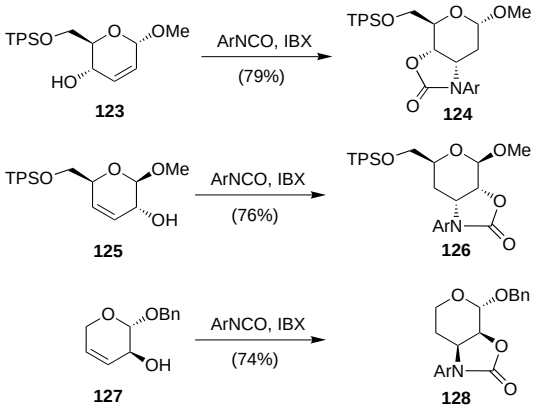
Table 8. Solution- and solid-phase synthesis of 2-deoxyorthoesters and 2,3-allylic orthoesters (see Scheme 30).[a][90]



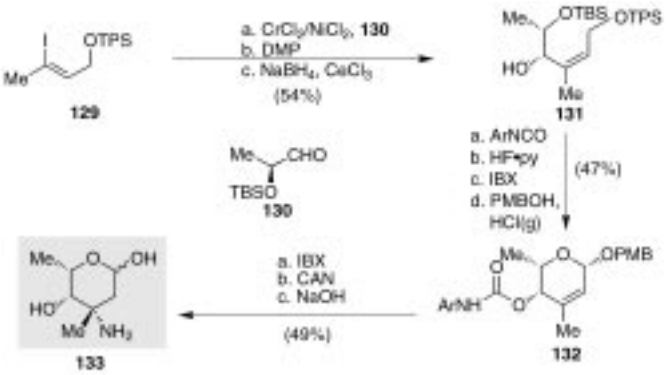
[a] Selenoxides were heated in a sealed tube at 140 °C in vinyl acetate/toluene/diisopropylamine (1/1/2) for 12 h (● = polystyrene).



Scheme 31. General concept for the IBX-mediated construction of amino sugars (2000).[91]



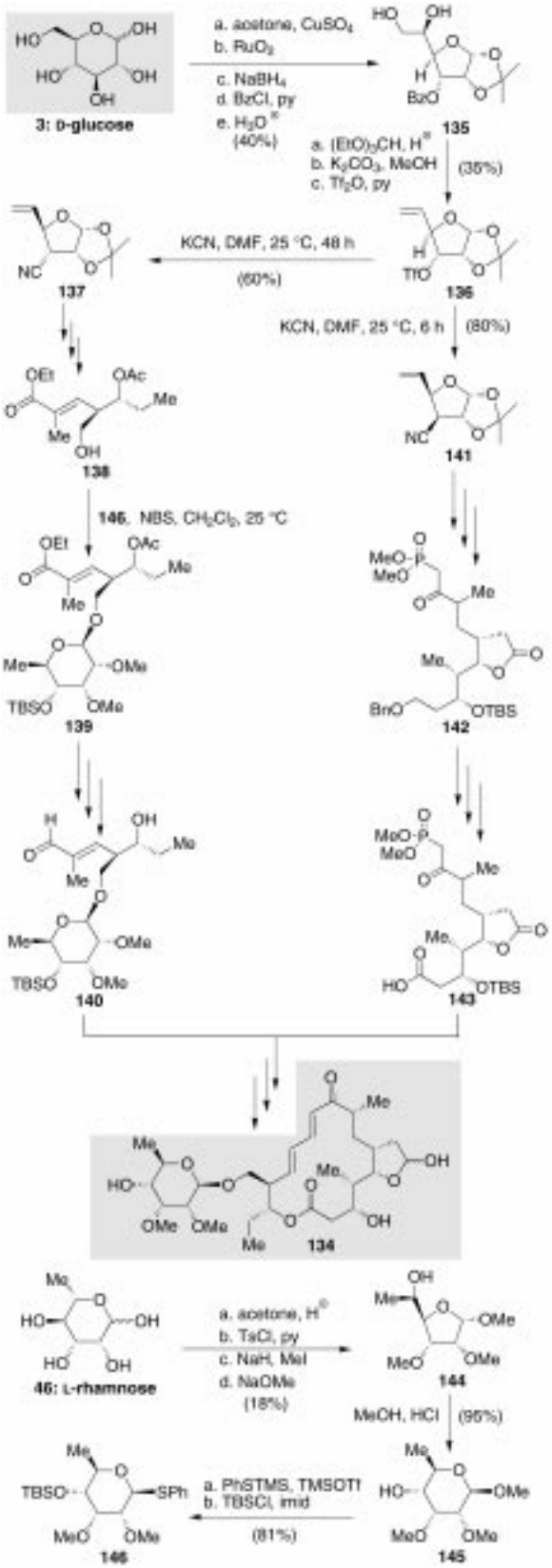
Scheme 32. Selected examples of the IBX-mediated construction of amino sugars (2000).[91]



Scheme 33. Synthesis of vancosamine (**133**) using the IBX method (2000).[91]

4.1. *O*-Mycinosyl Tylonolide

Within a program directed towards the synthesis of macrolide antibiotics, in particular tylosin and amphotericin, the total synthesis of *O*-mycinosyl tylonolide (**134**, Scheme 34) was accomplished; this marked the first synthesis of a tylosin assembly containing an intact carbohydrate moiety.[92] *O*-Mycinosyl tylonolide (**134**) is a major degradation product of tylosin and a potential biosynthetic and synthetic precursor to this antibiotic. The synthesis of this compound also falls within the scope of Section 2.1, in that the construction of the aglycon originated from carbohydrates. Thus, in a slightly modified procedure to that described for the synthesis of leucomycin A_3 and carbomycin B, D-glucose (**3**) was transformed to crystalline triflate derivative **136**, which was subsequently converted into unsaturated ester **138** and phosphonate **142** (Scheme 34). Thioglycoside **146** (derived from L-rhamnose (**46**)) was activated with NBS in CH_2Cl_2 in the presence of **138** to afford an approximately 50% yield of



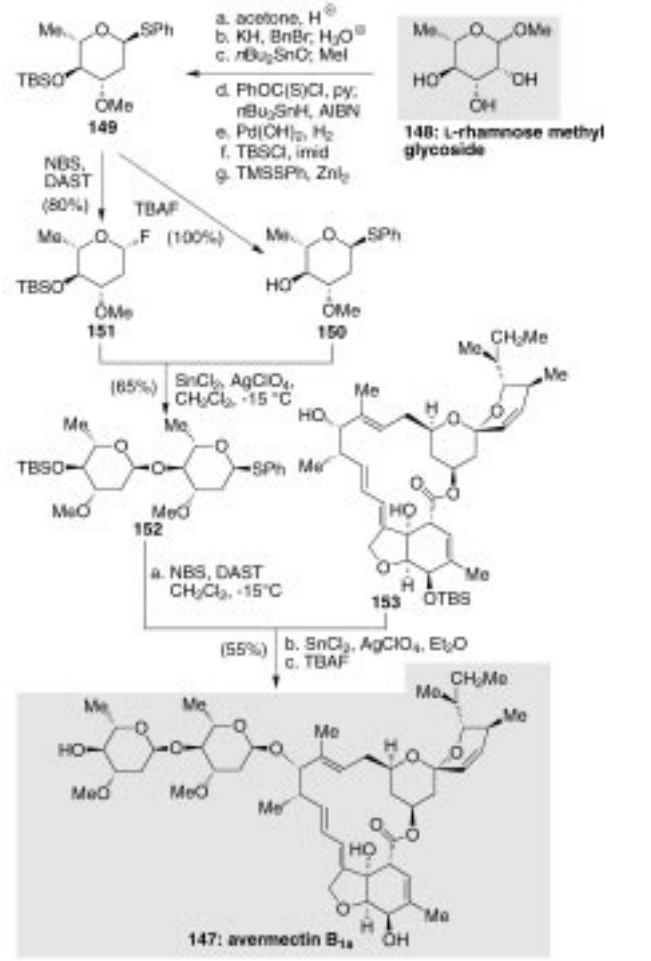
Scheme 34. Synthesis of *O*-mycinosyl tylonolide (**134**) from D-glucose (**3**) (1982).[92]

the desired β-anomer of the expected glycoside (**139**) after separation (α:β ratio, $\approx$2:3). This coupling represented the first use of NBS for activation of thiophenylglycosides under

such mild conditions. Further elaborations of these intermediates led to key building blocks **140** and **143**, which were then coupled and cyclized to afford the target, *O*-mycinosyl tylonolide (**134**), in high overall yield and good selectivity.

4.2. Avermectin B_{1a}

As a demonstration of the useful nature of the two-stage activation procedure using thioglycosides and glycosyl fluorides, a semisynthesis of avermectin B_{1a} (**147**, Scheme 35) was devised and accomplished in 1984.[9] L-rhamnose derivative

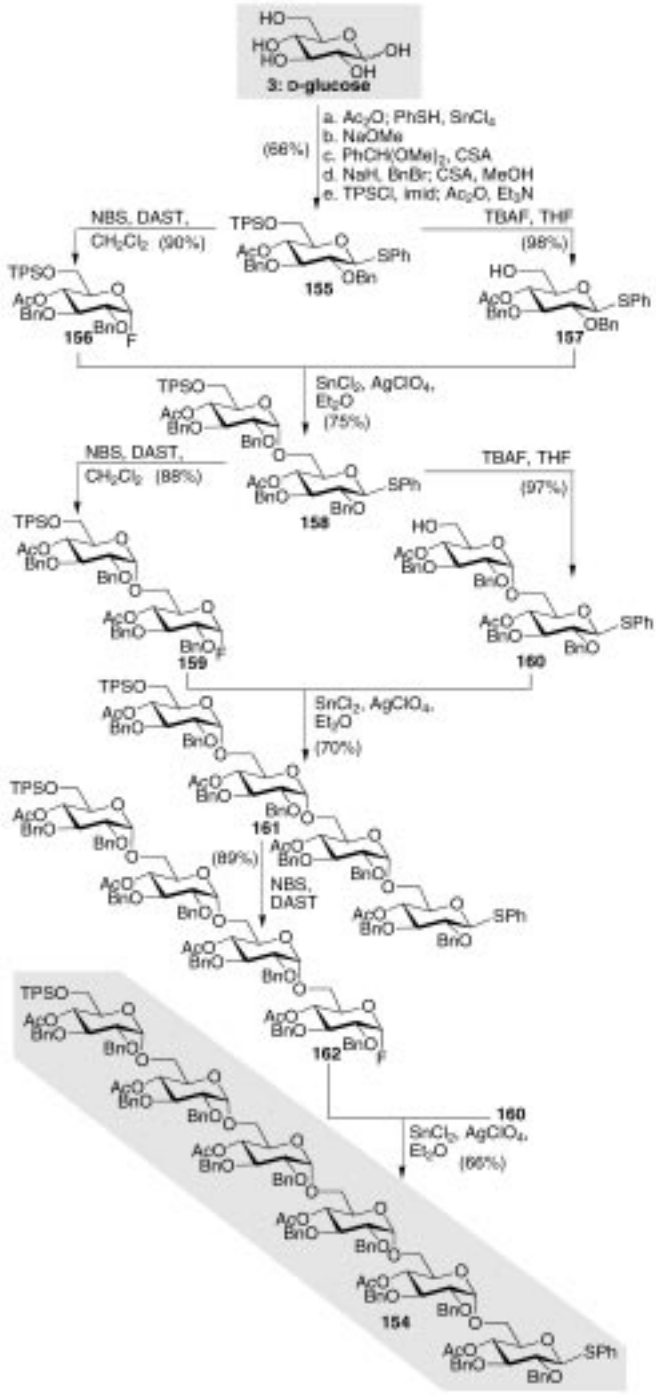


Scheme 35. Semisynthesis of avermectin B_{1a} (**147**) from L-rhamnose methyl glycoside (**148**) (1984).[9]

148 was converted into oleandrose derivative **149**, with selective acetal formation and tin acetal mediated protection methods; this was then transformed into hydroxy component **150** and to glycosyl fluoride **151**. Smooth coupling of these two units in the presence of $SnCl_2/AgClO_4$ afforded exclusively the α-anomer of disaccharide **152**. Activation of the disaccharide by conversion into the corresponding glycosyl fluoride (85%) and coupling to the aglycon **153** in the presence of $SnCl_2/AgClO_4$ (62%) was followed by deprotection (89%), to furnish avermectin B_{1a} (**147**), and thus complete a partial synthesis of this important antiparasitic agent.

4.3. Hexasaccharide 154

The hexasaccharide **154** (Scheme 36) was targeted in an effort to further demonstrate the repetitive and block-type nature of the two-stage activation technology for the synthesis of complex oligosaccharides. This linear chain, which consists of six glucose units linked in a 1,6 fashion, was constructed in 1984.[9] Thus, glucose derivative **155** was smoothly converted into free hydroxy derivative **157** and glycosyl fluoride **156**. Coupling of these two units in the presence of $SnCl_2/AgClO_4$



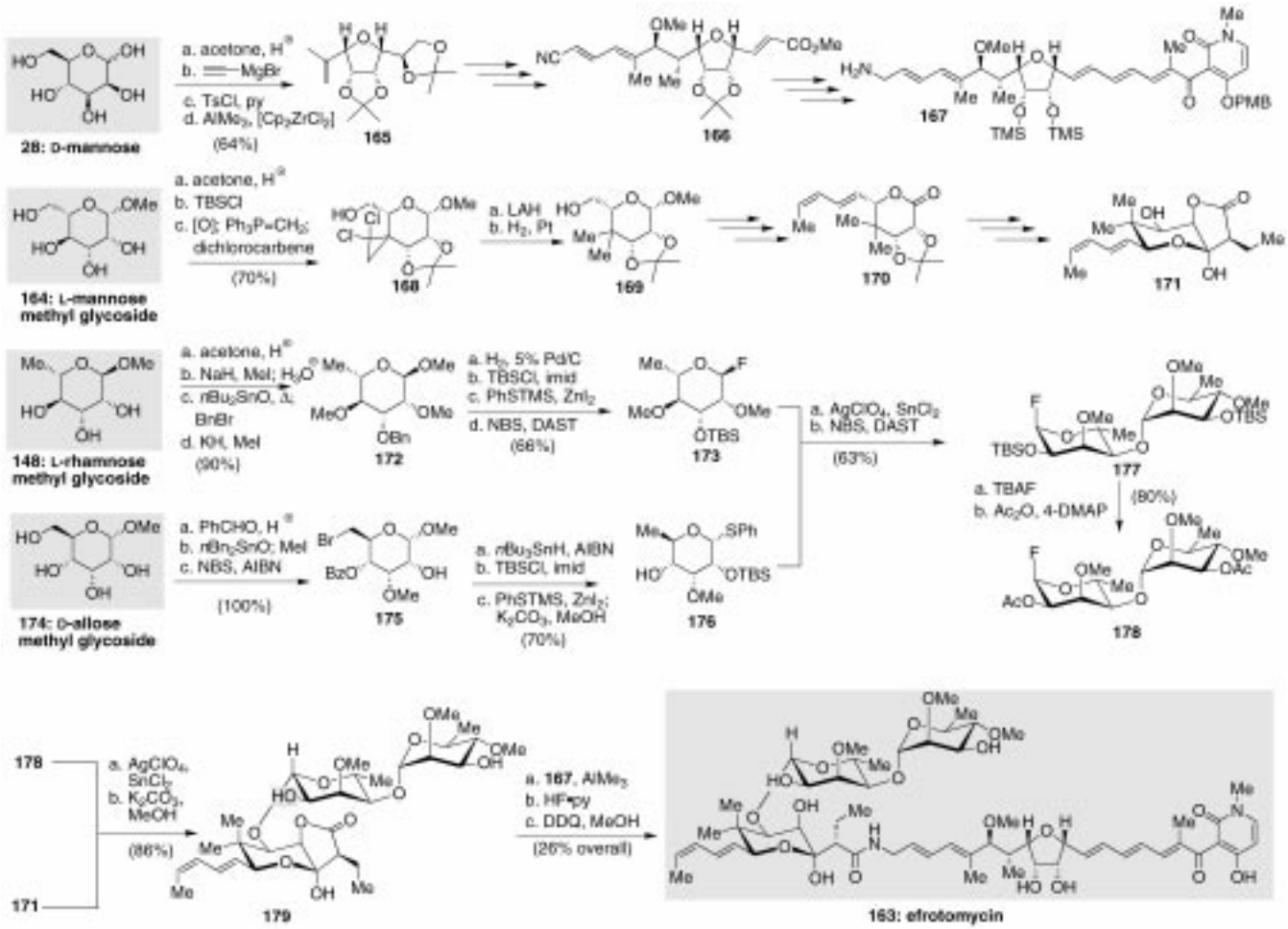
Scheme 36. Expedient synthesis of hexasaccharide **154** by the two-step activation procedure (1984).[9]

afforded the disaccharide **158** in 75% yield. Repetition of this sequence provided tetrasaccharide **161**, which was further elongated to hexasaccharide **154** in a highly efficient manner through one more reiteration of the process.

4.4. Efrotomycin

Efrotomycin (**163**, Scheme 37), isolated from *Nocardia lactamdurans*, is a member of the elfamycin class of narrow-spectrum antibiotics. The total synthesis of efrotomycin (**163**), reported in 1985,[93–96] included an efficient construction and attachment of the oligosaccharide domain onto the aglycon and several approaches to the goldinonolactone (**171**) and tetrahydrofuran (**167**) fragments, both from carbohydrate and noncarbohydrate starting materials.

Scheme 37 illustrates the synthesis of these key fragments using carbohydrates as chiral building blocks. D-Mannose (**28**) served as an excellent precursor to the tetrahydrofuran fragment (**167**), by providing three of the desired stereocenters and the functionality necessary for further elaboration. Thus, **28** was processed by conversion into the bisacetonide, reaction with excess ethinyl magnesium bromide, chemoselective formation of the tosylate resulting in internal displacement, and regioselective methylation with $AlMe_3$ in the presence of Cp_2ZrCl_2, to provide advanced intermediate **165**. Further elaboration effected the conversion of **165** into **167** and set the stage for the final coupling. The readily available L-mannose derivative **164**, which contains three of the five stereocenters of goldinonolactone (**171**), was recognized as a potential precursor to this intermediate. Thus, conversion of **164** into the monoacetonide, selective silylation, oxidation, olefination, and dichlorocarbene addition afforded adduct **168**. Sequential reduction to the geminal dimethyl compound, followed by oxidation and further homologation, afforded the complete fragment goldinonolactone (**171**). D-allose derivative **174** and L-rhamnose derivative **148** were sequentially transformed into the requisite coupling partners **176** and **173**, respectively (Scheme 37). Once again the efficiency of the two-stage activation procedure was illustrated as thioglycoside **176** and glycosyl fluoride **173** were smoothly coupled to afford the expected disaccharide. Transformation to glycosyl fluoride **177**, exchange of the C2 *O*-silyl group for a directing acetate group, and coupling with goldinonolactone fragment **171** proceeded to afford, after deacetylation, advanced intermediate **179**, as exclusively the desired β-anomer. Finally, union of the two key fragments **179**



Scheme 37. Synthesis of efrotomycin (**163**) from D-mannose (**28**), L-mannose methyl glycoside (**164**), L-rhamnose methyl glycoside (**148**), and D-allose methyl glycoside (**174**) (1985).[93–96]

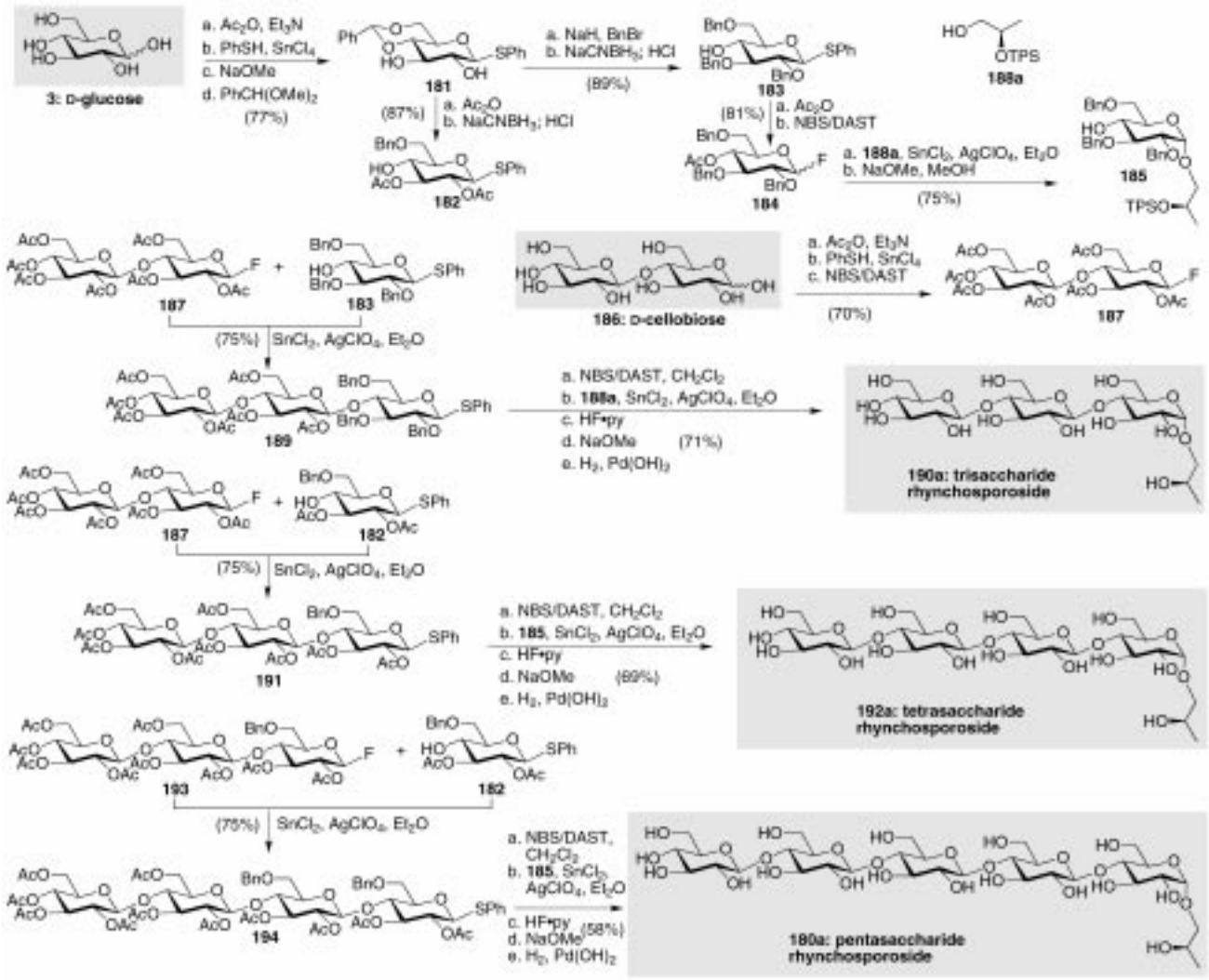
and **167** and final deprotection afforded the natural product, efrotomycin (**163**), in a highly convergent manner.

4.5. Rhynchosporosides

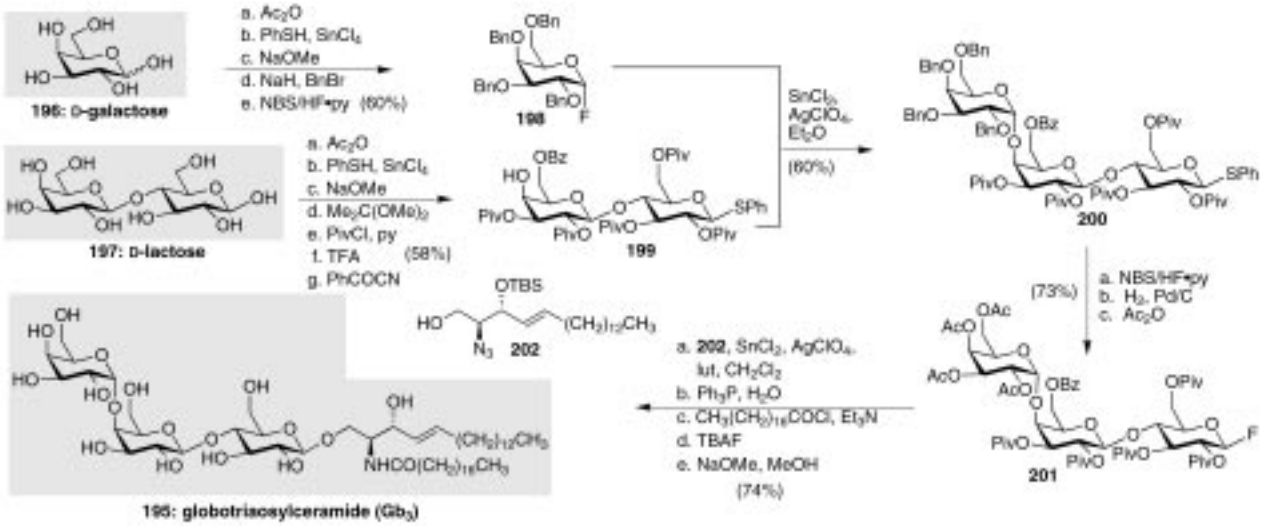
The rhynchosporosides (that is, **180a**, **190a**, and **192a**, Scheme 38) are a family of fungal metabolites which cause scald disease in barley and other grasses. In view of the potential economic importance of these compounds and in an effort to assist in their isolation from their natural sources, their structural elucidation, and investigations into their biological properties, a program directed towards their synthesis was undertaken. By strategically choosing the C2 substituent in each case, the mild, two-stage activation method allowed an efficient and convergent synthesis (completed in 1985,[97]) of both the *S* and *R* series of tri-, tetra-, and pentasaccharide rhynchosporosides (*S* and *R* refer to the configuration of the side chain; *R* series shown in Scheme 38). Preliminary bioassays with the synthetic samples indicated highly destructive potency for the (*3R*)-, (*4R*)-, and (*5R*)-rhynchosporosides (**190a**, **192a**, and **180a**) which caused massive tip wilt and necrosis in young barley plants.

4.6. Globotriaosylceramide (Gb_3)

Glycosphingolipids are key constituents of the membranes of most cell types and are recognized as fundamental mediators of cell–cell recognition and communication, cell-growth regulation, and antibody interactions. The biological significance of these cell-markers has made them important targets for isolation, characterization, and chemical synthesis. Their difficult accessibility from natural sources made the latter objective even more urgent. A program directed towards the synthesis of various glycosphingolipids in our laboratories grew to include many members of this class of bioactive natural products. The general methodology used in these constructions is exemplified by the total synthesis of globotriaosylceramide (Gb_3) (**195**, Scheme 39), whose total synthesis was completed in 1988.[98–100]



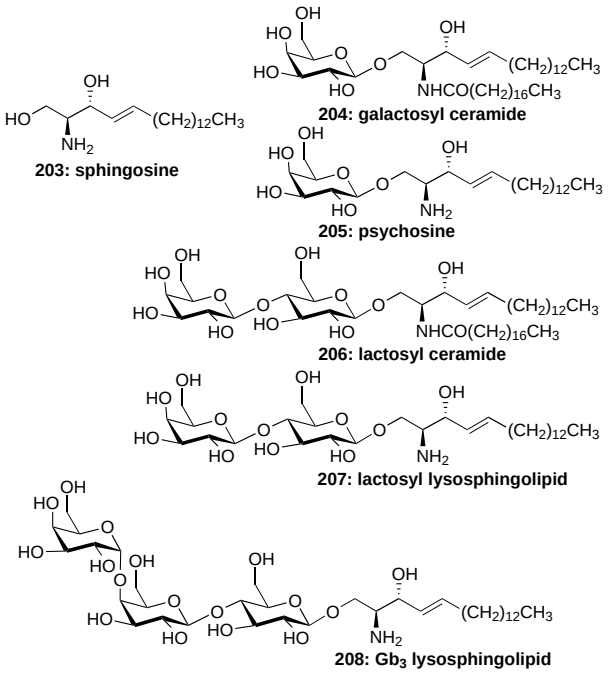
Scheme 38. Synthesis of rhynchosporosides **190a**, **192a** and **180a** (1985).[97] Compounds **190b**, **192b**, and **180b** (not shown) are the corresponding *S* compounds.



Scheme 39. Synthesis of globotriaosylceramide (Gb_3, **195**) from D-galactose (**196**) and D-lactose (**197**) (1988).[98–100]

The required coupling partners were glycosyl fluoride **198** and phenylthio glycoside **199** according to the planned two-stage activation procedure. These were prepared from D-galactose (**196**) and D-lactose (**197**) respectively, as outlined in Scheme 39. Coupling of **198** and **199** furnished trisaccharide **200**, which was then converted into the glycosyl fluoride (NBS/HF · py, 85%). The benzyl groups were then removed (H_2, Pd/C, 90%) and the resulting product was acetylated (Ac_2O, 95%); this illustrates the chemical stability of the glycosyl fluoride moiety. The coupling of trisaccharide fluoride **201** with sphingosine equivalent **202** under the usual conditions proceeded smoothly and with complete stereocontrol. Final elaboration of the sphingosine unit and global deprotections completed the synthesis of globotriaosylceramide (Gb_3) (**195**), whose assigned structure could therefore be confirmed.

This synthesis demonstrated the power of the overall strategy, which was now ready for extension to more complex glycosphingolipids. In collaboration with Fiore and co-workers at the Brigham and Women's Hospital and Harvard Medical School, synthetic sphingosine, lysosphingosine, and a number of glycosphingolipids were designed, synthesized, and evaluated as inhibitors of functional responses of human neutrophils. Seven compounds were synthesized (**195** and **203**–**208**, Scheme 40) following the chemistry described in Scheme 39. They were then studied for neutrophil responses in aggregation, leukotriene generation, and superoxide formation.[101] The results of these aggregation studies are illustrated graphically in Figure 1. Overall, the studies provided evidence that sphingolipids do not exhibit selective



Scheme 40. Synthetic sphingolipids **203**–**208** that were tested, along with **195**, for their ability to either inhibit or stimulate the aggregation of human neutrophils (1990). (See Figure 1.)

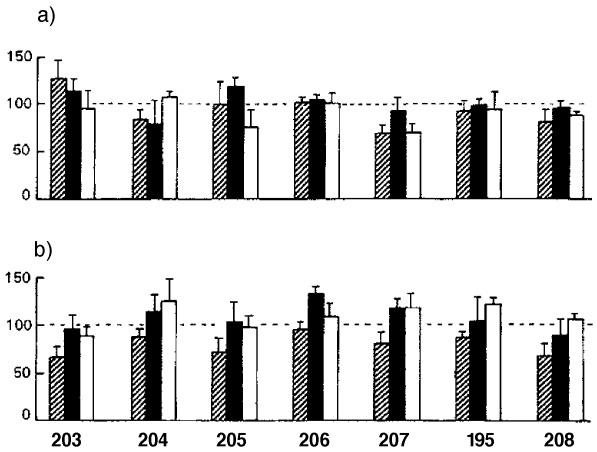


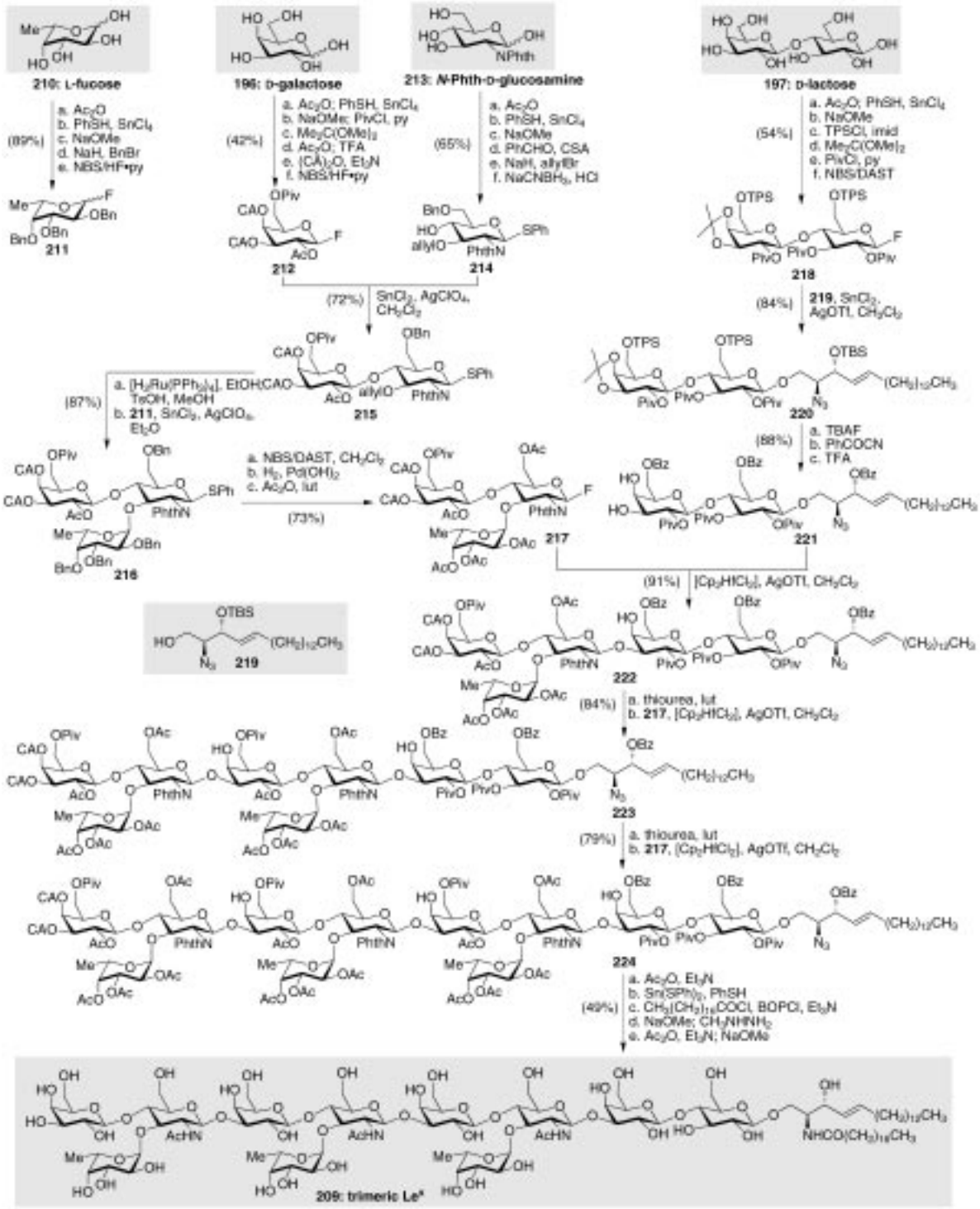
Figure 1. Aggregation response of human neutrophils: actions of synthetic sphingolipids (see Scheme 40) at noncytotoxic levels. Concentrations of the sphingolipids: ▨ = 1, ■ = 0.1, and □ = 0.01 μM. Conditions: 15 min, 37 °C in PBS (pH 7.45), then addition of either a) fMetLeuPhen (0.5 μM) or b) PMA (0.1 μM). Changes in light transmittance were monitored for 15 min. The results are expressed as percentage change in agonist-induced neutrophil aggregation (maximal 100%) after exposure to synthetic sphingolipids. Reproduced with permission from ref. [101].

inhibition of functional responses of human neutrophils, when added to intact cells

4.7. Trimeric Le^x

Glycosphingolipids carrying the Lewis antigen X (Le^x) determinant [gal-β-14-(fuc-α-13)-glcNAc] are known to accumulate in a wide variety of human cancers. Their extreme scarcity coupled with their potential applications in diagnostics and immunotherapy made them prime targets for chemical synthesis. In 1990, the total synthesis[102] of three members of this class of compounds (monomeric, dimeric, and trimeric Le^x) based on the two-stage activation procedure was reported from these laboratories.

Scheme 41 summarizes the synthesis of the most complex of the three, trimeric Le^x (**209**), in which careful selection of protecting groups allowed, not only for high selectivity in the



Scheme 41. Synthesis of trimeric Le^x (**209**) from D-galactose (**196**), L-fucose (**210**), D-lactose (**197**), and *N*-phthaloyl-D-glucosamine (**213**) (1990).[102]

sequence, but also for exclusive formation of the desired stereochemistry of all glycoside bonds. The coupling of lactosyl fluoride **218** (obtained from D-lactose as shown in Scheme 41) and sphingosine equivalent **219** afforded glycoside **220**, and was followed by further functionalization, to furnish lactosyl ceramide segment **221**. The construction of the Le^x trisaccharide intermediate **217** proceeded from the readily available glucosamine derivative **214** and galactosyl fluoride intermediate **212**, whose origins were traced back to *N*-phthaloyl-D-glucosamine (**213**) and D-galactose (**196**), respectively. Coupling of **212** and **214** furnished disaccharide **215**, and was followed by selective removal of the allyl group and subsequent coupling with fucosyl fluoride **211** (obtained from L-fucose (**210**) as indicated) to afford trisaccharide **216**. Conversion of thioglycoside **216** into the glycosyl fluoride with NBS/DAST, followed by protecting group exchange, furnished the requisite trisaccharide fragment **217**. The coupling of **217** and **221** under the influence of AgOTf/$[Cp_2HfCl_2]$[12b] proceeded regioselectively at the more reactive C3 position to afford β-pentasaccharide **222**. Selective removal of the monochloroacetate groups from **222** was accomplished with thiourea in 93% yield. Reiteration of the deprotection and coupling procedure with another molecule of glycosyl fluoride **217** led sequentially to octasaccharide **223** and finally undecasaccharide **224**. Generation of trimeric Le^x (**209**) from **224** proceeded smoothly as indicated. The completion of this synthesis demonstrated the practicality of the two-stage activation procedure in highly complex situations and provided significant quantities of this important glycosphingolipid for potential diagnostic and therapeutic applications.

4.8. Sialyl Le^x

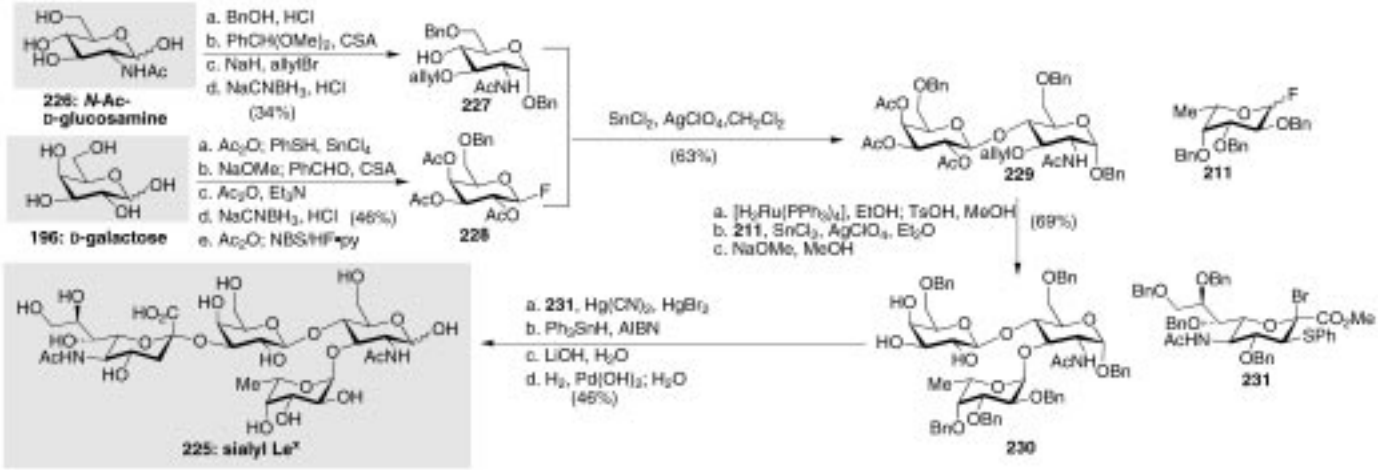
Identification of sialyl Le^x type molecules as binding ligands of ELAM-1 (endothelial leukocyte adhesion molecule 1) generated considerable excitement given the connection of ELAM-1 to inflammation and related disorders. Sialyl Le^x (**225**, Scheme 42) and sialyl dimeric Le^x (derivative **232** shown in Scheme 43) are ELAM-1 binding ligands, which have also been identified as tumor-associated oligosaccharides. As such, and in view of potential therapeutic and tumor-cell marking applications, these molecules became high-priority targets for chemical synthesis immediately following their identification. The total synthesis of sialyl Le^x (**225**), reported from these laboratories in 1991, relied on the thiophenyl group to facilitate and control β-2-deoxyglycoside formation.[103]

Monomeric Le^x component **230** was synthesized (Scheme 42) by modification of the chemistry developed in the synthesis of trimeric Le^x (**209**) (described above, Scheme 41). Thus, key building blocks **227** and **228** (derived from *N*-acetyl-D-glucosamine (**226**) and D-galactose (**196**), respectively, by regioselective benzylidene acetal cleavage reactions) were coupled to provide disaccharide **229** in 63% yield. Removal of the allyl group from **229**, followed by coupling with L-fucose derivative **211** and deacetylation, afforded triol **230**. Selective coupling with sialic derivative **231** in the presence of $Hg(CN)_2/HgBr_2$, followed by reductive removal of the thiophenyl group and global deprotection, afforded sialyl Le^x (**225**).

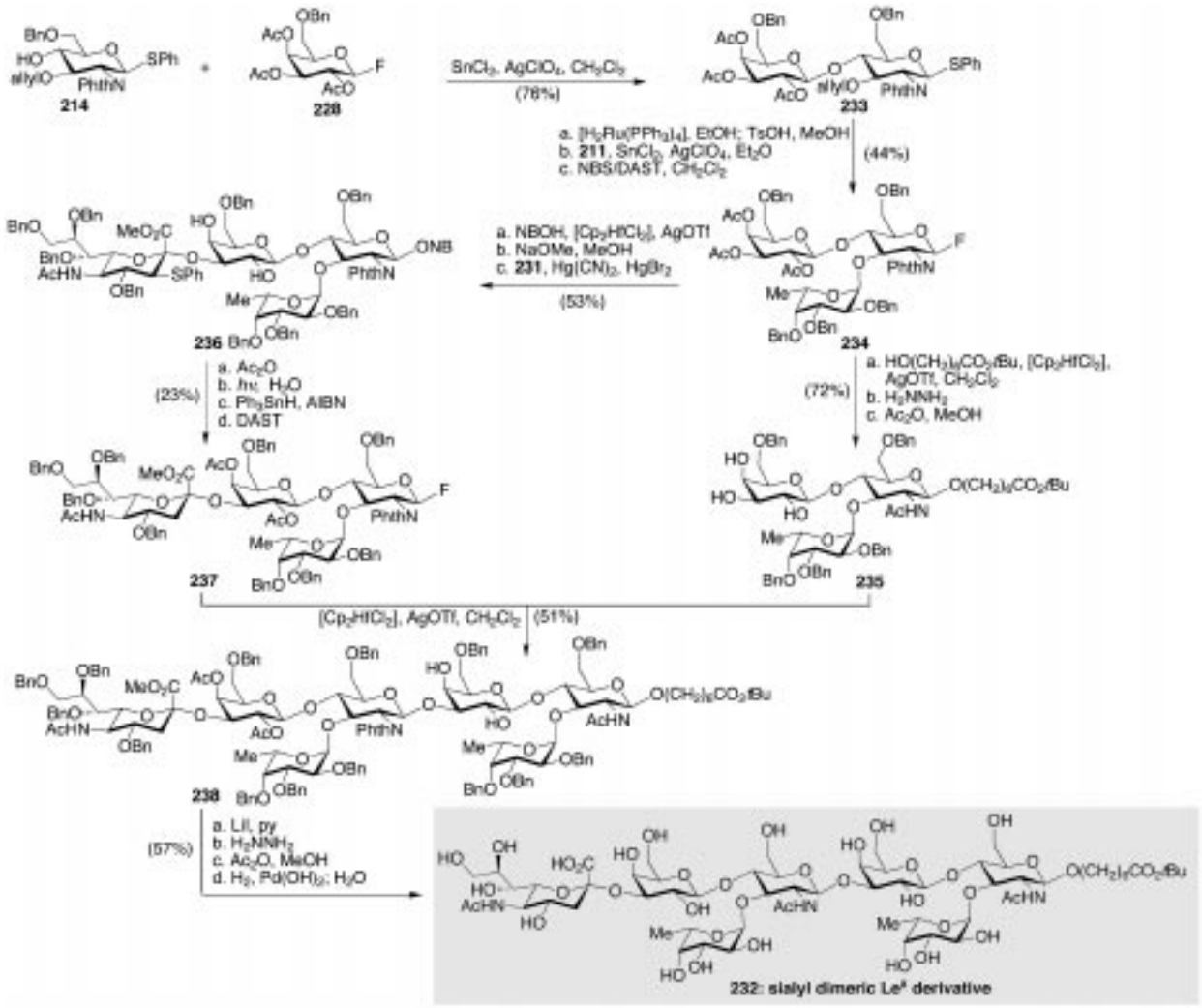
In order to further understand the structure–function relationship of sialyl Le^x and to develop sialyl Le^x mimetics, conformational studies based on two-dimensional NMR techniques were performed, in combination with MM2 molecular mechanics, in collaboration with the Wong group at Scripps.[104] In addition, and in collaboration with the same group, the Ca^{2+} binding properties of the sialyl Le^x and deoxygenated fucose analogues were examined by pneumatically assisted electrospray mass spectrometry, and provided evidence that Ca^{2+} is coordinated primarily to the GalGlcNAc moiety of sialyl Le^x.[105, 106]

4.9. Sialyl Dimeric Le^x

Among the naturally occuring ELAM-1 binding oligosaccharides, sialyl dimeric Le^x occupies a prominent position due to its molecular complexity and potential as a highly potent substrate. The total synthesis of sialyl dimeric Le^x derivative **232** (Scheme 43), equipped with an anchoring device for



Scheme 42. Synthesis of sialyl Le^x (**225**) from *N*-acetyl-D-glucosamine (**226**), D-galactose (**196**), L-fucose (**210**), and sialic acid derivative **231** (1991).[103]



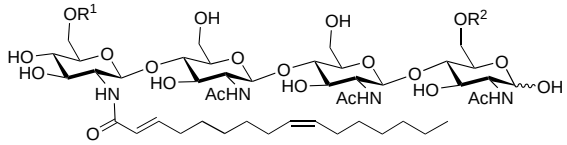
Scheme 43. Synthesis of sialyl dimeric Le^x derivative **232** from *N*-phthaloyl-D-glucosamine (**213**), D-galactose (**196**), L-fucose (**210**), and sialic acid derivative **231** (1992).[107]

further chemical and biological studies, was reported from these laboratories in 1992.[107] Trisaccharide fluoride **234** was synthesized by modification of the chemistry developed in the synthesis of sialyl Le^x described above and was a key building block for the rapid and convergent assembly of the sialyl dimeric Le^x skeleton.

Thus, as shown in Scheme 43, trisaccharide fluoride **234** was converted into trihydroxy compound **235** by glycosidation, deacetylation, and *N*-acetylation. Compound **234** was also converted into sialylic derivative **236** by glycosidation with nitrobenzyl alcohol (94%), deacetylation (98%), and coupling with sialic acid derivative **231** (56%) to afford, regio- and stereoselectively, tetrasaccharide **236**. Acetylation of the remaining hydroxyl groups, photolytic cleavage of the *O*-nitrobenzyl glycoside system, radical cleavage of the thiophenyl group, and finally treatment with DAST resulted in the formation of tetrasaccharide fluoride **237**. Glycosylation of triol **235** with tetrasaccharide fluoride **237** again proceeded regioselectively to afford the heptasaccharide **238**. Global deprotection furnished the targeted sialyl dimeric Le^x derivative **232** in pure form for biological investigations.

4.10. NodRm-IV Factors

Nodulation factors (Scheme 44) are important signaling molecules involved in the symbiosis between bacteria of the family *Rhizobium* and legumes. They are typically sulfated



239: NodRm-IV factor (Ac, S) R^1 = Ac, R^2 = SO_3^-
240: NodRm-IV factor (S) R^1 = H, R^2 = SO_3^-
241: NodRm-IV factor (Ac) R^1 = Ac, R^2 = H
242: NodRm-IV factor R^1 = H, R^2 = H

Scheme 44. Structures of selected NodRm-IV factors.

lipooligosaccharides of *N*-acetyl-D-glucosamine (**226**). Secreted by the microorganism *Rhizobium meliloti*, these molecules elicit the formation of nitrogen-fixing root nodules. They display high specificity in that sulfated NodRm-IV factors **239** and **240** are active only on alfalfa, whereas nonsulfated

NodRm-IV factors **241** and **242** are active only on pea and vetch. The synthesis of the most challenging member of this group of naturally occurring substances, NodRm-IV (Ac, S; **239**), is presented in Scheme 45.[108]

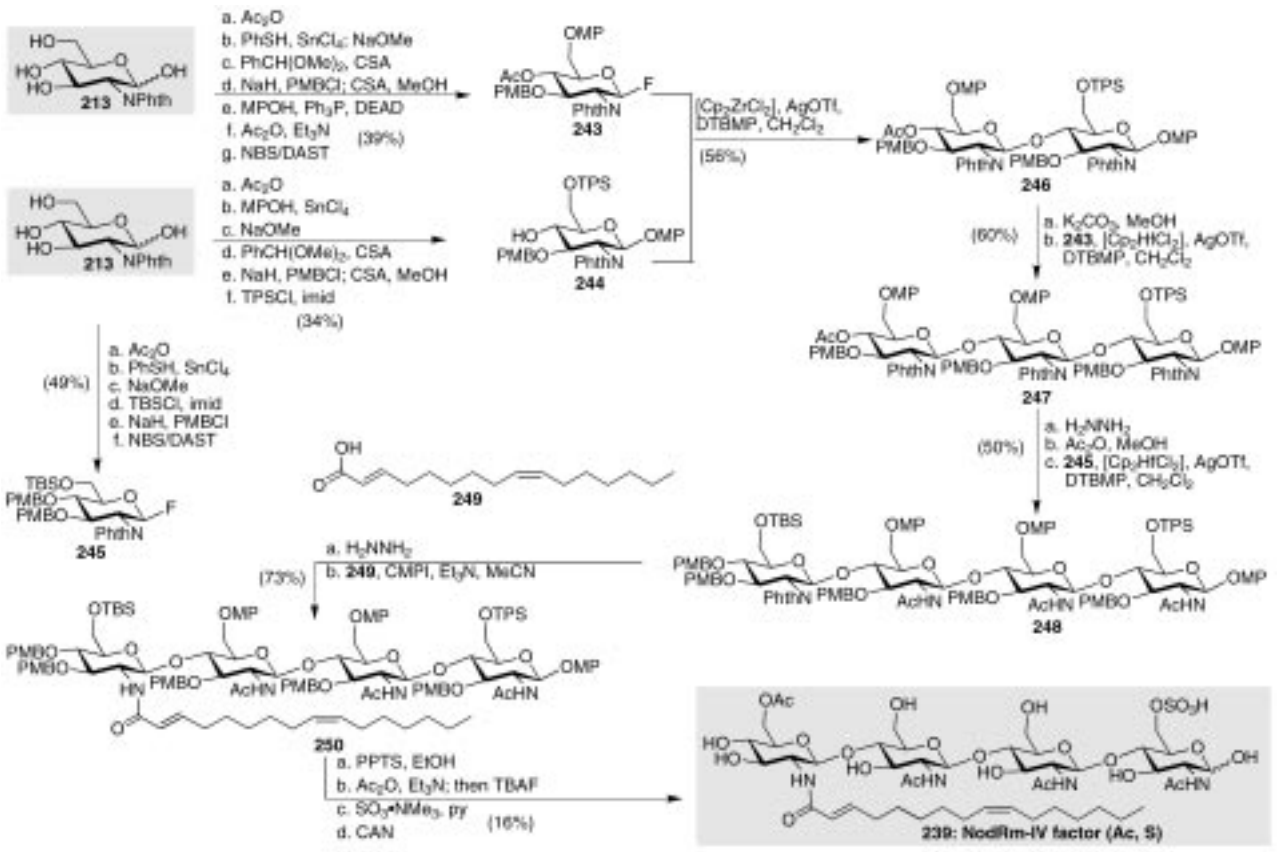
The strategy required careful design of protecting group tactics in order to incorporate the required functionality into the repeated units. Thus, coupling of glucosamine derivative **243** (obtained from *N*-phthaloyl-D-glucosamine **213** as shown) and glycosyl fluoride **244** (also obtained from **213**) furnished disaccharide **246**. The acetyl group was then removed and the coupling procedure was repeated to afford trisaccharide **247**. The directing phthalimide moieties were then replaced with acetyl groups and the resulting hydroxy trisaccharide was coupled with an additional unit of glycosyl fluoride **245**, to furnish tetrasaccharide **248** stereoselectively. Generation of the free amine, followed by incorporation of the fatty acid chain **249**, generated the fully protected derivative **250**. Selective deprotections and installation of the acetyl and sulfate groups completed the synthesis of this biologically interesting molecule, rendering it available for biological studies.

A version of NodRm-IV (Ac, S; **239**) that was tritiated across the C9–C10 olefin of the acyl side chain was chemically synthesized.[109] Its binding characteristics were studied in collaboration with Cullimore's group at Toulouse and were found to be consistent with a single class of binding sites.[109] Competition with modified Nod factors indicated that the binding was independent of the *O*-acetyl, the sulphate group, or the degree of unsaturation on the fatty acid. However, both the side-chain and the oligosaccharide moieties were required for high affinity binding. More recently, Demont-Caulet et al. have synthesized NodRm-IV factors with acyl side chains of different length and unsaturations and studied their effects on nodule formation.[110]

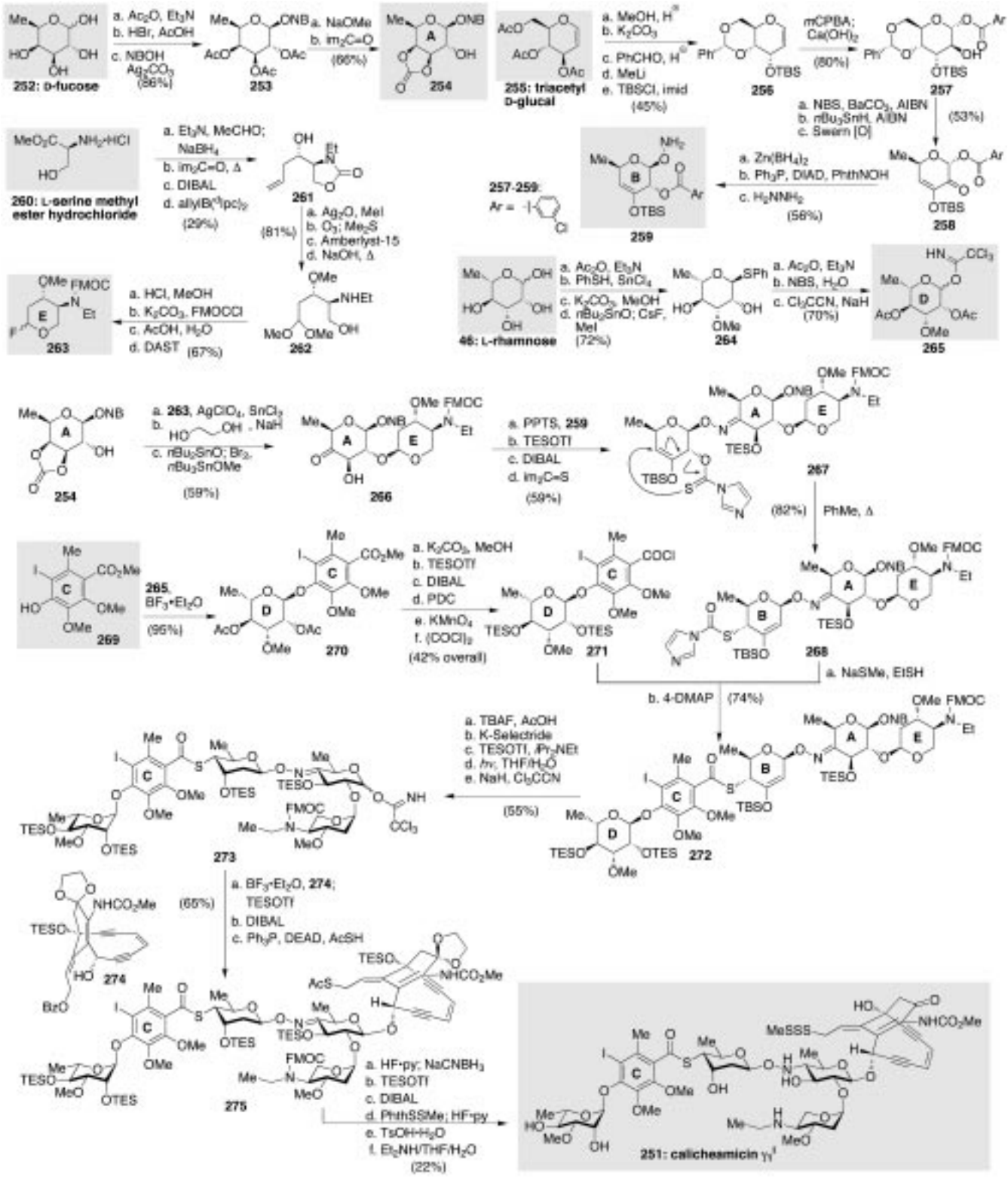
4.11. Calicheamicin γ_1^I

In 1987, a new class of antitumor antibiotics, the enediynes, was reported and led to considerable excitement in the chemical and biological communities. The molecular structure of calicheamicin γ_1^I (**251**, Scheme 46), one of the first to be disclosed and amongst the most prominent members of the class, embodies a rigid dioxygenated bicyclic core containing a 1,5-diyn-3-ene (enediyne) system and a single, but highly unusual, oligosaccharide appended at C8 which includes an oxyimino glycosidic linkage and an iodinated, hexasubstituted thiobenzoate unit. While the key elements to the biological activity of calicheamicin γ_1^I (**251**) lie within its enediyne core and the series of events eminating from it, which lead to DNA destruction in tumor cells by Bergman cyclization, the oligosaccharide domain serves important roles in delivery and recognition, in that it binds to duplex DNA with remarkable selectivity, particularly to TCCT, TCTC, and TTTT sequences.

Our total synthesis of calicheamicin γ_1^I (**251**) reported in 1992 includes a considerable body of carbohydrate chemistry as highlighted in Scheme 46.[111–122] Retrosynthetic analysis of



Scheme 45. Synthesis of NodRm-IV factor **239** from *N*-phthaloyl-D-glucosamine (**213**) (1992).[108]



Scheme 46. Synthesis of calicheamicin γ_1^I (**251**) from D-fucose (**252**), L-rhamnose (**46**), triacetyl-D-glucal (**255**), and L-serine methyl ester hydrochloride (**260**) (1992).[111–122]

the oligosaccharide portion suggested that synthesis of the central B-ring subunit would be the most challenging, as it contained the oxyimino linkage to ring A, a sulfur atom at position C4, and deoxygenated positions at C2 and C6. In light of the sensitive nature of this fragment, a novel approach involving a [3,3]-sigmatropic rearrangement of a thionoimidazolide carrying an enol ether was developed to install both the sulfur atom and to deoxygenate the C2 center. The required building blocks **254**, **259**, **263**, **265**, and **269** were constructed as shown in Scheme 46 from D-fucose (**252**),

triacetyl-D-glucal (**255**), L-serine methyl ester hydrochloride (**260**), L-rhamnose (**46**), and 3,4,5-trimethoxytoluene, respectively. Of particular note during these sytheses was the epoxidation and opening of intermediate **256** with *m*CPBA, followed by the radical cleavage of the benzylidene acetal with NBS, migration of the aryl ester, and glycosidation under Mitsunobu conditions, finally affording enol ether **259**. In addition, the use of $n\mathrm{Bu_2SnO}$ to selectively protect the C3 position of the D ring in the synthesis of intermediate **265** is noteworthy.

The assembly of the desired oligosaccharide began with the coupling of ring A, compound **254**, with glycosyl fluoride **263** (corresponds to ring E) to afford the targeted AE disaccharide; this was deprotected (NaH, ethylene glycol) and selectively oxidized to hydroxyketone **266** with the highly useful tin acetal technology in 59% overall yield. The latter compound (**266**) was then condensed with aminooxyglycoside **259** in the presence of PPTS to afford the corresponding oxime (single isomer, configuration not assigned), which was further subjected to silylation, DIBAL reduction, and thionoimidazolide formation to afford substrate **267**. Thermal treatment of **267** in toluene at 110 °C induced the expected [3,3]-sigmatropic rearrangement, which led to thiocarbamate **268** in high overall yield. Alternatively, coupling of phenol **269** with trichloroacetimidate **265** was smoothly promoted with $\mathrm{BF_3 \cdot Et_2O}$, to furnish glycoside **270** stereoselectively. Further elaboration of **270** led to acid chloride **271**, whose coupling with the thiol derived from **268** (NaSMe, EtSH) proceeded under the influence of 4-DMAP and $\mathrm{Et_3N}$ to afford pentacyclic system **272**. The silyl enol ether of the latter compound was selectively cleaved (TBAF, AcOH) and the resulting ketone was reduced stereoselectively (K-Selectride) to the α-hydroxy compound; this was then silylated, photolytically deprotected at the reducing end, and activated as a trichloroacetimidate in high overall yield, ready for attachment to the aglycon portion of the molecule. The latter goal was accomplished when the trichloroacetimidate **273** was coupled to aglycon **274** to furnish, after DIBAL reduction and Mitsunobu reaction (AcSH, $\mathrm{Ph_3P}$, DEAD), compound **275**. Final elaboration of **275** in six steps led to calicheamicin γ_1^{I} (**251**).

In collaboration with Paloma and Chazin at the Scripps Research Institute, extensive 1D and 2D ^{1}H NMR studies were undertaken to establish the molecular basis for the mode of DNA binding of **251** and to probe the origins of the sequence selectivity of the interaction between this potent antitumor antibiotic and DNA.[123, 124] Comparative analysis of the DNA complex formed with and without the aglycon demonstrated the critical role of the oligosaccharide domain in the molecular interactions leading to binding and sequence-specific recognition in the minor groove of the DNA duplex. In addition, in collaboration with Joyce from the same institute, the sequence-specific DNA cleavage activity of **251** was studied using a synthetic 20-mer DNA substrate that contained a single TCCT–AGGA target site (Figure 2). As expected, cleavage of the target DNA occured at a single, preferred site within the radiolabeled strand, corresponding to the 5′-C residue within the TCCT sequence (Figure 3).[125, 126]

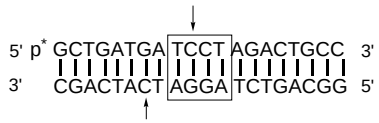


Figure 2. Synthetic 20-mer duplex DNA containing a single TCCT–AGGA target site (boxed region) for recognition by calicheamicin. Arrows denote sites of calicheamicin-induced DNA cleavage.[125]

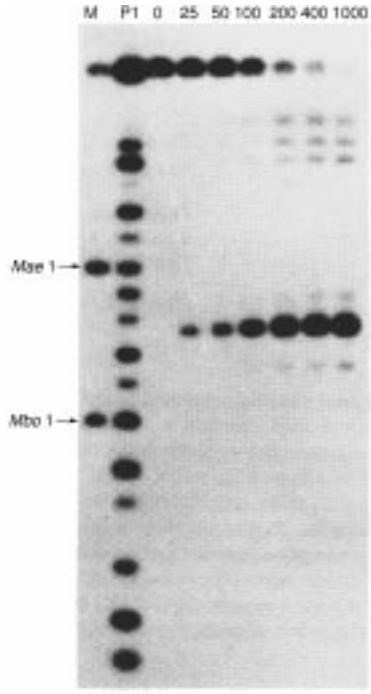


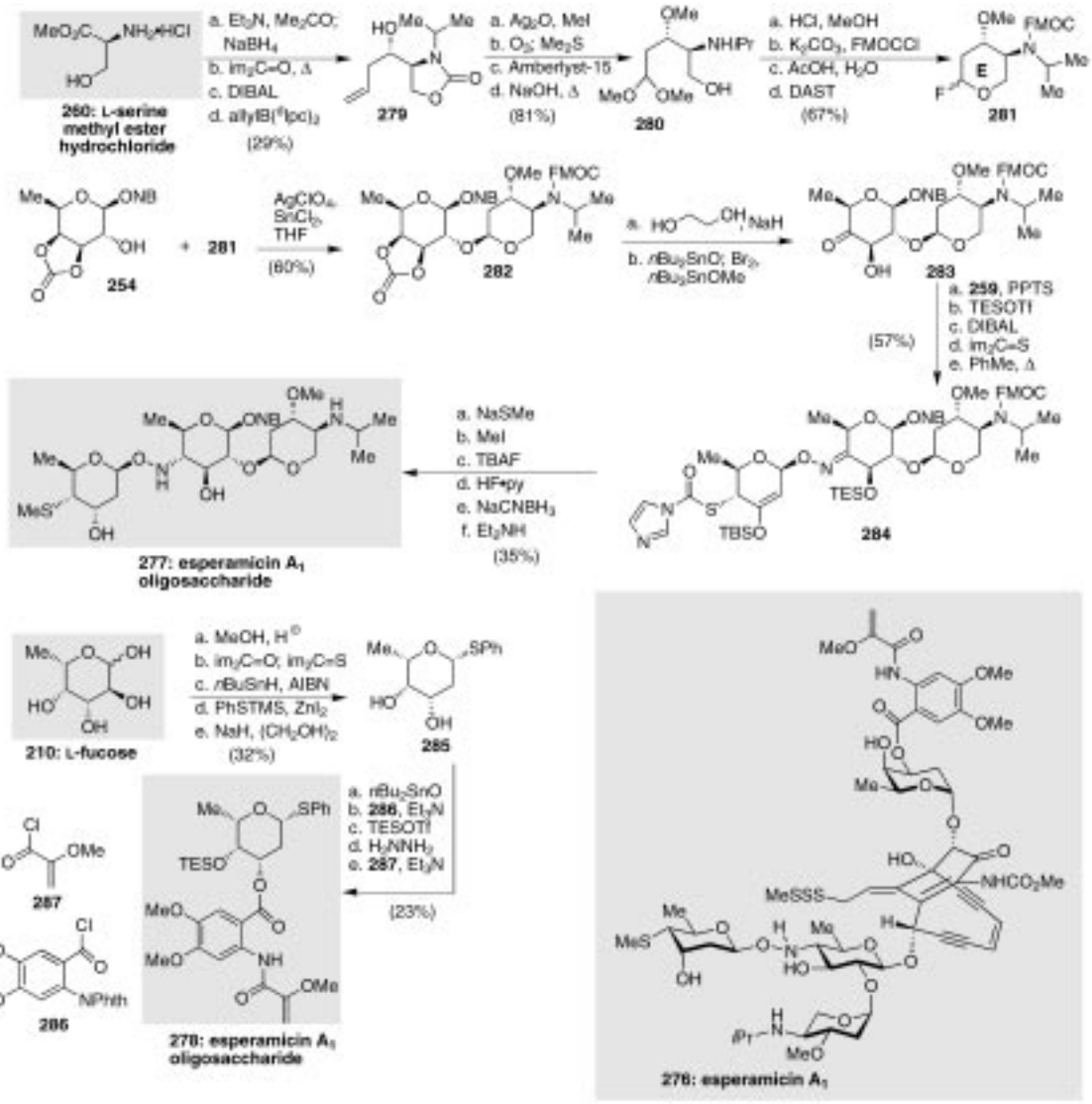
Figure 3. Autoradiogram of a denaturing polyacrylamide gel showing products of calicheamicin-induced DNA cleavage with the [5′-^{32}P]-labeled, TCCT-containing strand. M: marker lane containing an equimolar mixture of the products of DNA digestion with either *Mae*I (cleaves 5′-CTAG) or *Mbo*I (cleaves 5′-GATC) restriction enzymes. P1: oligonucleotide ladder resulting from partial DNA digestion with P1 nuclease (generates 3′-OH termini). Lanes 0–1000: products of DNA digestion in the presence of calicheamicin γ_1^{I} (concentrations: 0–1000 nM; incubation at 37 °C for 6 min). Reproduced with permission from ref. [125].

4.12. Esperamicin $\mathrm{A_1}$ Carbohydrate Domains

The carbohydrate units of esperamicin $\mathrm{A_1}$ (**276**) have also been synthesized (Scheme 47), with similar strategies to those for calicheamicin γ_1^{I} (**251**, Scheme 46).[127, 128] Thus, ring A alcohol **254** was coupled with the modified ring E fluoride **281** to afford disaccharide **282**. Processing of **282** proceeded in a similar manner as before to afford thioester **284** in high overall yield. Thioester cleavage, methylation, deprotection, and finally, oxime reduction afforded the fully deprotected esperamicin $\mathrm{A_1}$ trisaccharide **277**. The second oligosaccharide, **278**, was derived from L-fucose (**210**) and acyl chlorides **286** and **287**, as depicted in Scheme 47.

4.13. Sulfated $\mathrm{Le^x}$ and $\mathrm{Le^a}$

The recognition of the important roles of selectins in the recruitment of leukocytes to inflammation sites through

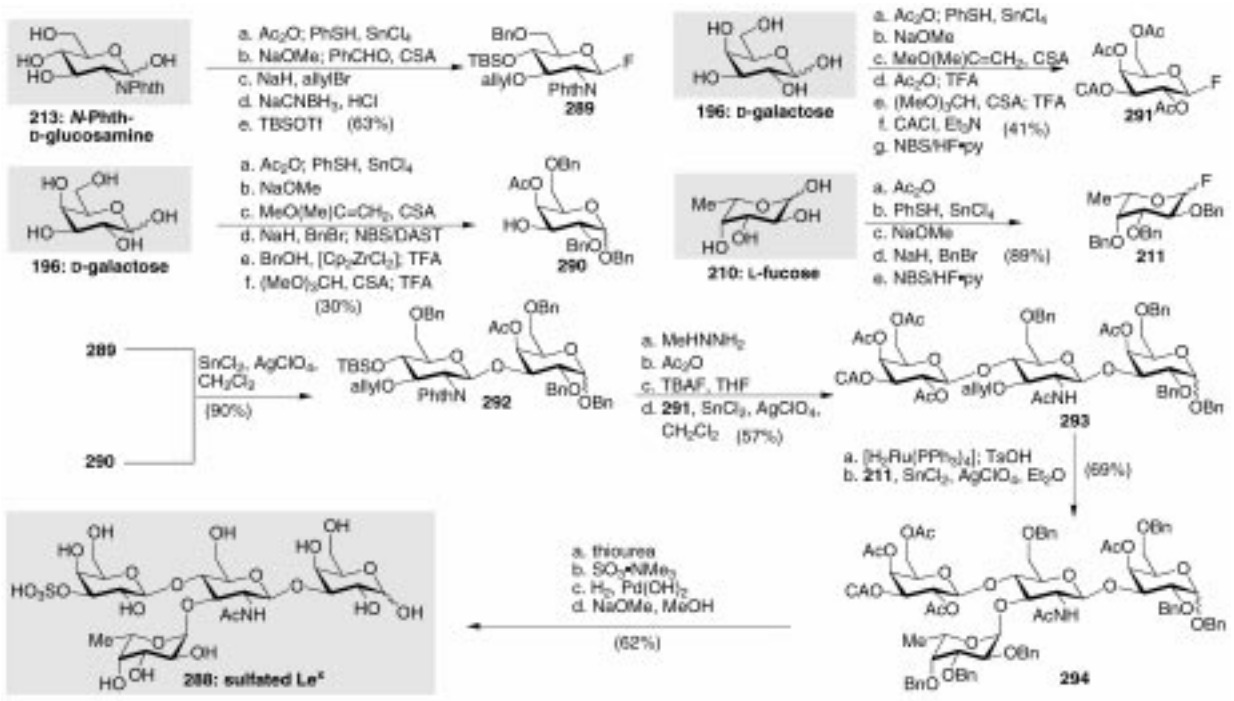


Scheme 47. Synthesis of esperamicin A_1 oligosaccharides **277** and **278** from D-fucose (**252**), triacetyl-D-glucal (**255**), L-fucose (**210**), and L-serine methyl ester hydrochloride (**260**) (1992).[127, 128]

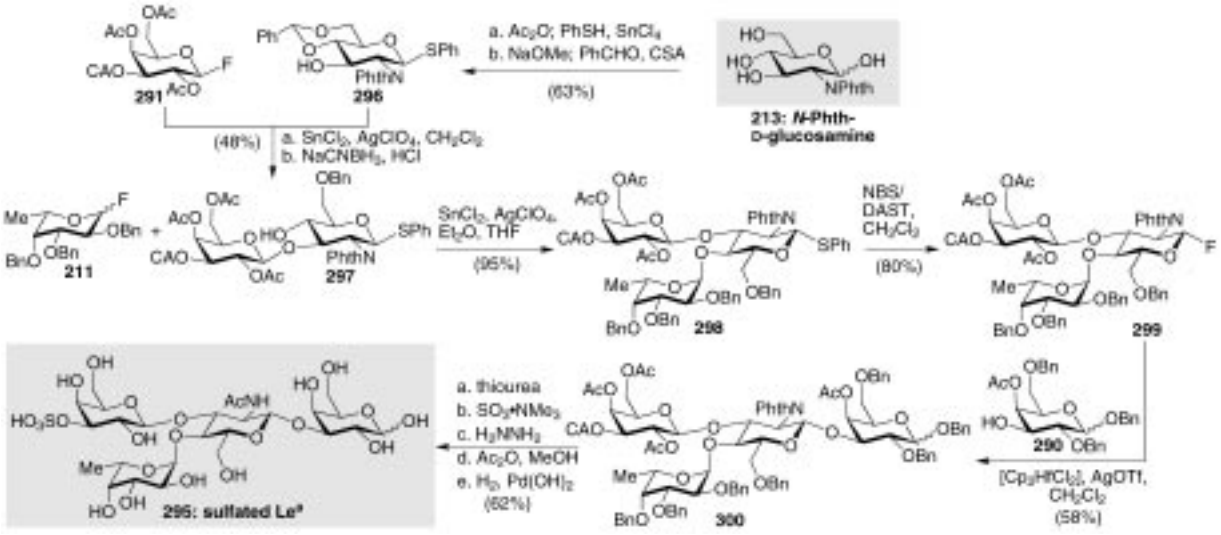
vascular adhesion has evoked extensive studies in this field over the last few years. Such studies led to the isolation and identification of the two sulfated tetrasaccharides, **288** (sulfated Le^x) and **295** (sulfated Le^a), as naturally occurring ligands for E-selectin with binding affinities similar to that of the sialylated compound (sialyl Le^x). The potential of these compounds in biology and medicine made them prime targets for chemical synthesis. In 1993 we reported the first total synthesis of **288** and **295** as well as their trisaccharide analogues **301** and **302** (see Scheme 50). Scheme 48 summarizes the synthesis of sulfated Le^x (**288**) that utilizes glycosyl fluoride chemistry in the key coupling processes.[129] Thus, the four required building blocks (**289**–**291** and **211**) were synthesized from *N*-phthaloyl-D-glucosamine (**213**), D-galactose (**196**), and L-fucose (**210**). Glycosyl fluoride **289** and alcohol **290** were coupled to afford, stereoselectively, disaccharide **292**, in which the phthalimide was subsequently exchanged for an acetate, and then the TBS was cleaved to enable coupling with glycosyl fluoride **291** to afford trisaccharide **293**. The allyl group was removed from **293** and the fourth carbohydrate moiety (**211**) was introduced stereoselectively to form **294**. Finally, selective removal of the trichloroacetate was followed by sulfation and deprotection to furnish sulfated Le^x (**288**) in high overall yield.

The sulfated Le^a compound **295** was constructed as shown in Scheme 49. The starting carbohydrates were the same as for **288** but the sequence was modified by judicial choice of protecting groups, reagents, and conditions to provide the final target in good overall yield. In this case, the selective opening of a benzylidene acetal was performed on a disaccharide, leading directly into the coupling with the next monosaccharide unit. Notable, once again, is the admirable performance of the two-stage activation procedure in this synthesis.

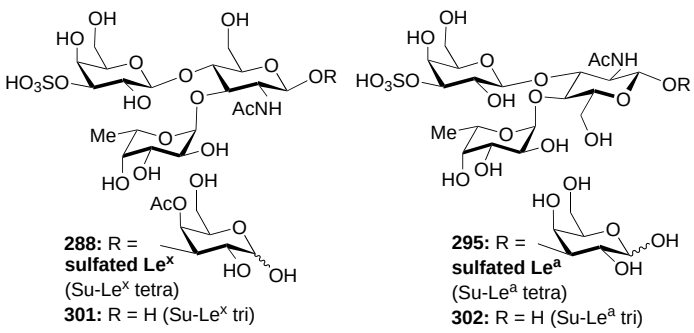
The chemically synthesized sulfated Le^x (**288** and **301**) and Le^a (**295** and **302**; Scheme 50) oligosaccharides were investigated in collaboration with Feizi's group,[130] in addition to other Le oligomers. Their ability to support E-selectin binding when converted into neoglycosphingolipids, as well as their ability to inhibit E-selectin binding to immobilized lipid-



Scheme 48. Synthesis of sulfated Le^x (**288**) from D-galactose (**196**), L-fucose (**210**), and *N*-phthaloyl-D-glucosamine (**213**) (1993).[129]



Scheme 49. Synthesis of sulfated Le^a (**295**) from D-galactose (**196**), L-fucose (**211**), and *N*-phthaloyl-D-glucosamine (**213**) (1993).[129]



Scheme 50. Synthesized and biologically evaluated (see Figure 4) sulfated Le^x (**288**, **301**) and Le^a (**295**, **302**) molecules (1993).

linked sialyl Le^a, Le^x, and sulfated Le^a pentasaccharides was studied. Initial results established that sulfated Le^a tetra- and pentasaccharides were the most potent oligosaccharide ligands for human E-selectin. Later studies[131] targeted the binding specificity of the leukocyte-adhesion molecule L-selectin (leukocyte homing receptor) towards the structurally defined sulphated oligosaccharides. The results are shown in Figure 4.

4.14. Heptasaccharide Phytoalexin Elicitor (HPE)

Heptasaccharide phytoalexin elicitor (HPE, **303**, Scheme 51) is a naturally occurring substance isolated from

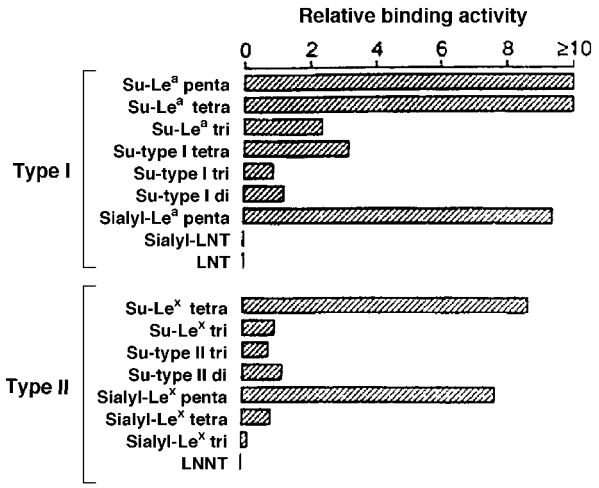
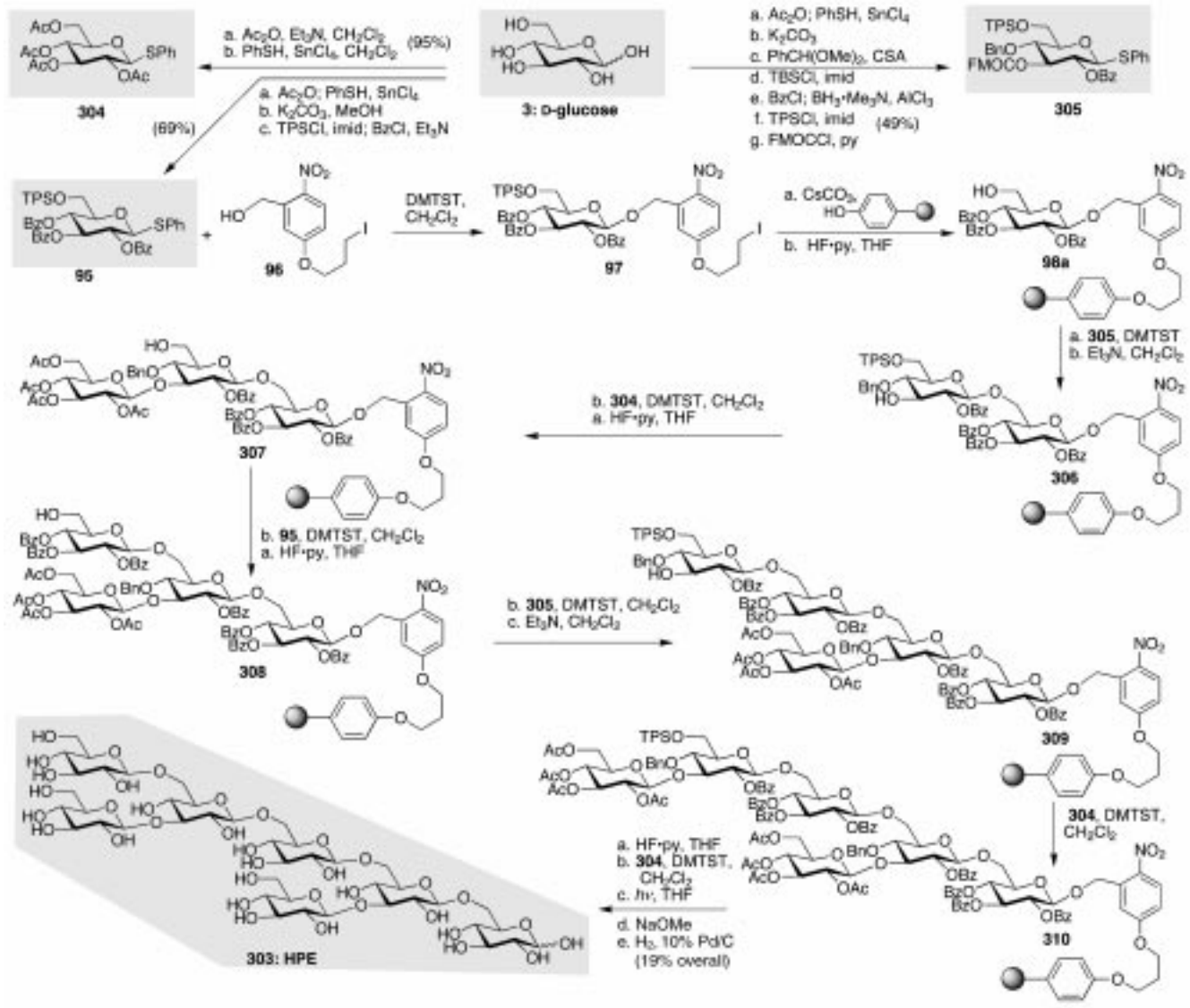


Figure 4. Relative L-selectin binding affinities of lipid-linked oligosaccharides (see Scheme 50), investigated with the quantitative microwell binding assay. Binding affinities relative to the binding affinity of sulphated Le^x trisaccharide (Su-Le^X tri) were calculated from binding curves. Reproduced with permission from ref. [131].

the mycelial walls of the fungus *Phytophthora megasperma*. Exhibiting potent phytoalexin elicitor activity with nanomolar binding properties toward its receptor, HPE (**303**) was the first natural product to be synthesized on solid phase by this group and, at that time (1997), represented the largest branched oligosaccharide ever constructed on solid support from monosaccharide units in a reiterative manner.[87] This target molecule presented an ideal opportunity to test the applicability of the novel phenolic polystyrene-based photolabile linker strategy described in Section 3 (Scheme 26).

Thus, D-glucose (**3**) was converted into the three required building blocks **95**, **304**, and **305** by standard chemistry, and compound **95** was coupled with **96** and linked onto the resin (→98, see Scheme 26) to afford conjugate **98a** upon desilylation. Carbohydrate unit **305** was then coupled onto the growing oligosaccharide chain to furnish, after removal of the FMOC group, monohydroxy compound **306**, whose reiterative elaboration to resin conjugate **310** proceeded through intermediates **307**–**309**. From **310** the targeted HPE deriva-

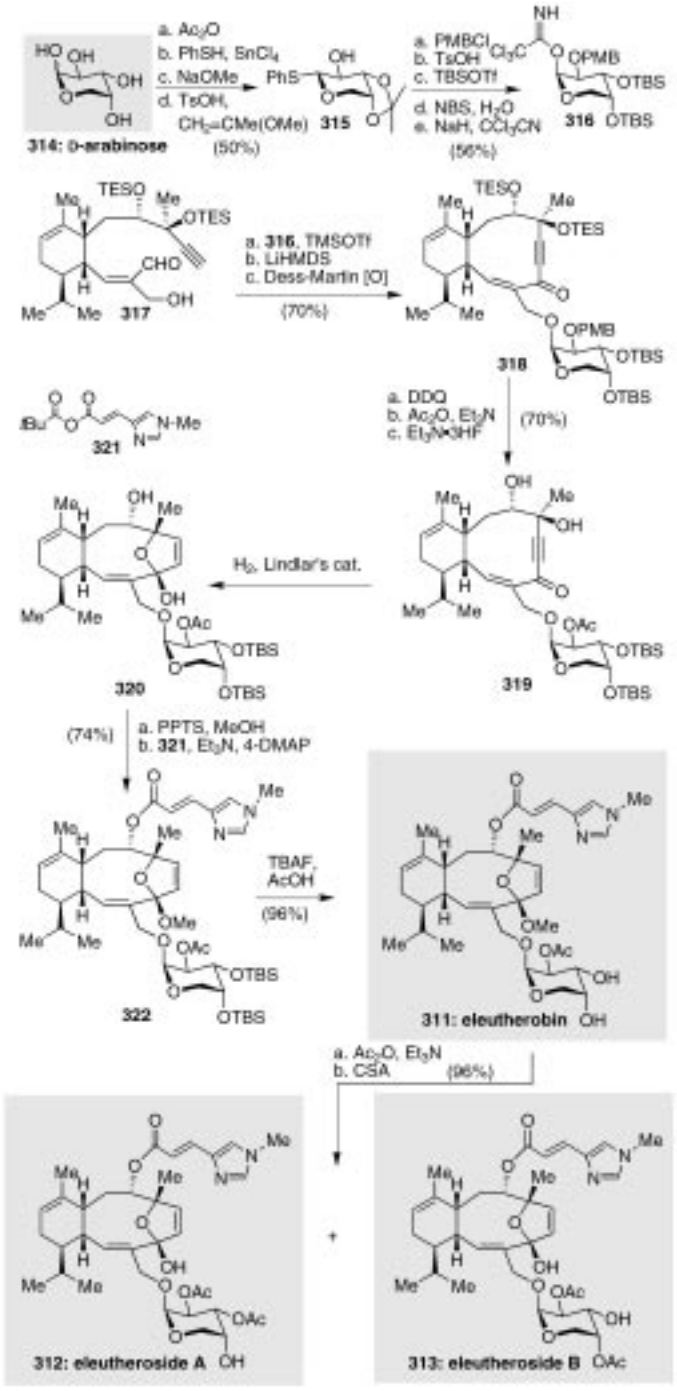


Scheme 51. Solid-phase synthesis of heptasaccharide phytoalexin elicitor (HPE, **303**) from D-glucose (**3**) (1997).[87]

tive (**303**) was generated by desilylation, attachment of the final carbohydrate unit (**304**), photolytic cleavage, and removal of the protecting groups (19 % overall yield).

4.15. Eleutherobin

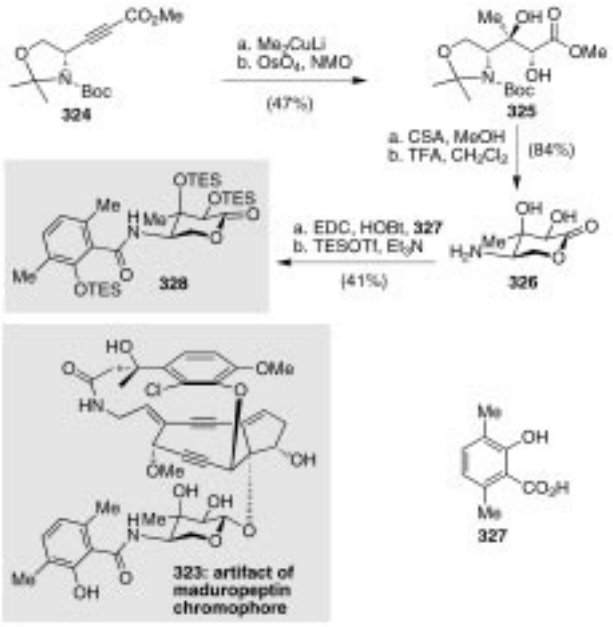
Eleutherobin (**311**, Scheme 52) is a recently discovered antitumor agent isolated from an *Eleutherobia* species of soft corals and exhibiting a taxol-like mechanism of action in polymerizing and stabilizing microtubules. The total syntheses of eleutherobin (**311**) and its relatives, eleutherosides A (**312**) and B (**313**), were completed in these laboratories in 1997; this allowed confirmation of the absolute stereochemistry and paved the way for library construction and chemical biology studies.[132–135] All three natural products contain acetylated arabinose moieties. Thus, D-arabinose (**314**) was converted into trichloroacetimidate derivative **316** via thioglycoside **315**, by employment of selective acetonide formation and a nonparticipating PMB group at the C2 position. Compound **316** was then coupled to primary alcohol **317** through the catalytic action of TMSOTf to afford, predominantly, the desired β-glycoside (54 % yield). Upon ring closure by the corresponding acetylide and oxidation, the 10-membered ring ketone **319** was obtained and was further elaborated to eleutherobin (**311**), eleutheroside A (**312**), and eleutheroside B (**313**).



Scheme 52. Synthesis of eleutherobin (**311**) and eleutherosides A (**312**) and B (**313**) from D-arabinose (**314**) (1997).[132–135]

4.16. Maduropeptin Chromophore Carbohydrate Domain

Maduropeptin, a complex of macromolecular antibiotics, was isolated from the broth filtrate of *Actinomadura madurae* in 1991. It was reported that maduropeptin consists of a 1:1 complex of an acidic, water soluble 32 kDa carrier protein and a nine-membered ring enediyne chromophore that possesses impressive antibacterial and antitumor properties. The naked chromophore proved to be too labile for isolation; but in the presence of methanol, an artifact of maduropeptin, compound **323** (Scheme 53), was isolated and characterized. As a prelude to a total synthesis of maduropeptin, madurosamine derivative **328** representing the carbohydrate domain of this architecturally unusual natural product, was constructed from the D-serine derived intermediate **324**, as summarized in Scheme 53.[136, 137]



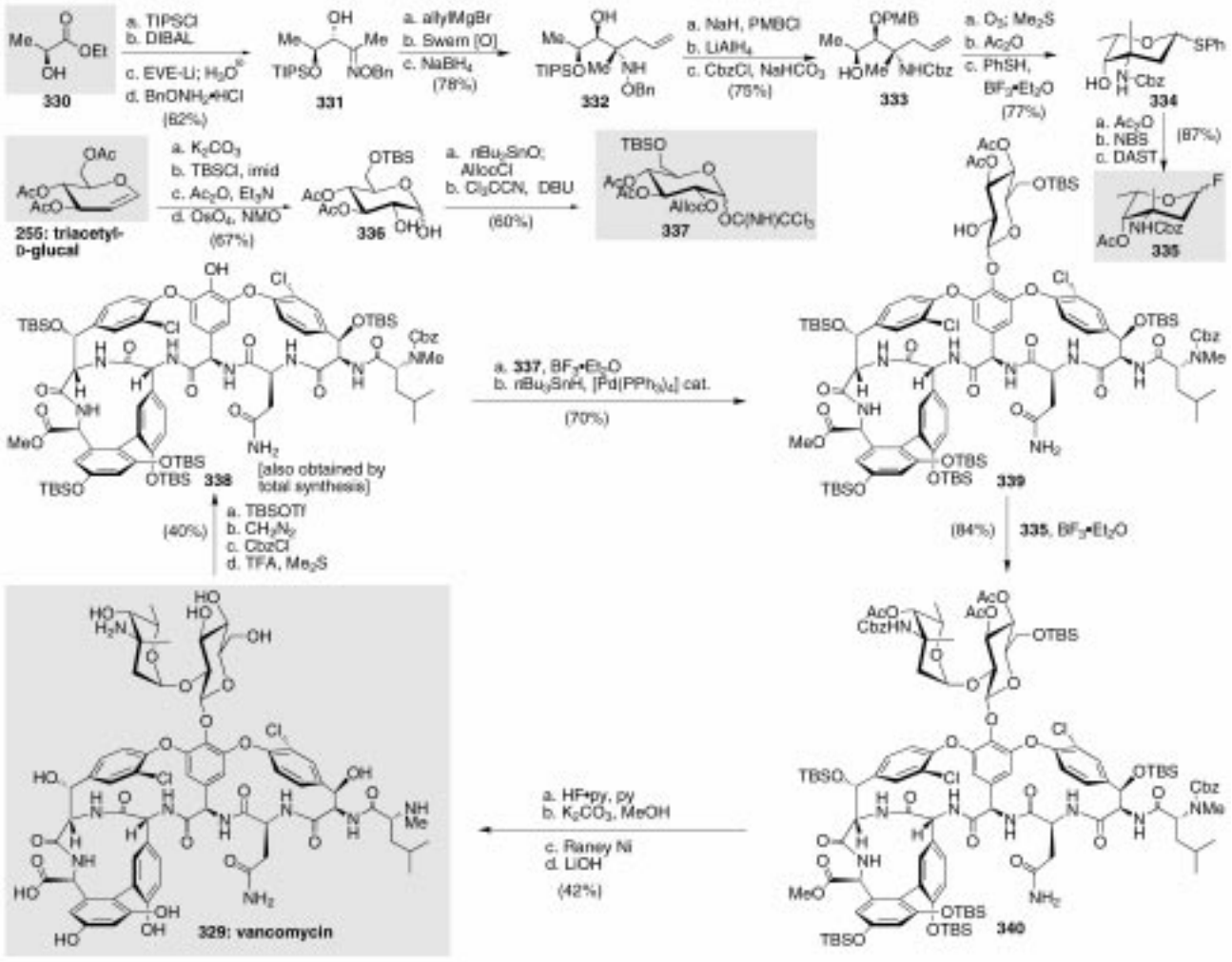
Scheme 53. Synthesis of madurosamine derivative **328** of the artifact of maduropeptin chromophore (**323**) from D-serine derivative **324** (1997).[136, 137]

4.17. Vancomycin

Vancomycin (**329**, Scheme 54), isolated from the fermentation broths of *Streptomyces orientalis*, belongs to a rather large class of antibiotics collectively known as glycopeptide antibiotics. It is used clinically as a last line of defense against resistant strains of Gram positive bacteria, particularly methicillin resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococcus* species. Vancomycin's mode of action includes binding to the D-Ala-D-Ala terminus of the growing peptidoglycan framework of the cell wall, and subsequent inhibition of transglycosidation (polymerization) and transpeptidation (cross-linking) so causing cell lysis.[138]

Vancomycin (**329**) possesses a unique molecular architecture, consisting of a disaccharide moiety (a glucose and a vancosamine) attached onto a rigid cyclic heptapeptide framework, aglycon (**338**). The sugar moieties play important roles in delivering these antibiotics to their targets by enhancing their solubility. The strategy for the final stages of the total synthesis of vancomycin (**329**) included reaction of a suitably protected vancomycin aglycon acceptor with appropriately functionalized glucose and vancosamine donors. It was proposed that a participating group at C2 of the glucose moiety could facilitate β-glycosidation, and that the anomeric effect could influence the glycosidation to deliver the required α-glycoside bond linking the two sugar units.

Model studies proved instrumental in developing the final plan for the total synthesis of vancomycin (**329**), which involved a stepwise glycosidation approach utilizing acceptor **338** and donors **337** and **335** (Scheme 54). The required building blocks **337** and **335** were synthesized from triacetoxy-D-glucal (**255**) and ethyl L-lactate (**330**), respectively, and then attached onto the aglycon sequentially. Thus, glycosidation of phenol **338** with excess trichloroacetimidate **337** in CH_2Cl_2 and in the presence of $BF_3{\cdot}Et_2O$ at $-78\,^{\circ}C$ proceeded smoothly to afford the monosaccharide in 82% yield. The C2 hydroxyl group of the glucose moiety was liberated by reaction with nBu$_3$SnH/[Pd(Ph$_3$P)$_4$] in wet CH_2Cl_2, leading to the new glycoside acceptor **339** (85% yield). The second glycosidation was achieved by treatment of alcohol **339** with glycosyl fluoride **335** in CH_2Cl_2 and in the presence of $BF_3{\cdot}Et_2O$ at $-35\,^{\circ}C$ to afford the fully protected vancomycin derivative **340** in 84% yield and with an approximately 8:1 ratio of α:β stereoselectivity. Chromatographically separated **340** was then subjected to desilylation (excess HF · py/py) and deacetylation (K_2CO_3 in MeOH), to form the Cbz-protected vancomycin methyl ester (95% yield). Finally, treatment with Raney Ni in nPrOH:H_2O (2:1) caused removal of the Cbz



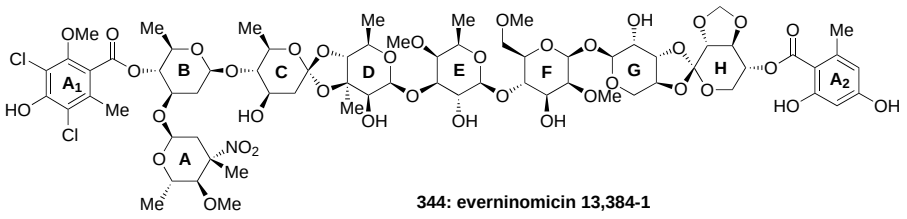
Scheme 54. Synthesis of vancomycin (**329**) from triacetoxy-D-glucal (**255**) and L-ethyl lactate (**330**) (1999).[139–141]

groups (without dechlorination), and subsequent saponification of the resulting vancomycin methyl ester with LiOH in THF:H_2O (1:1) at 0 °C furnished vancomycin (**329**) in 85% yield. Further studies with vancomycin led to a novel degradation strategy to transform vancomycin (**329**) into protected aglycon derivative **338**, by silylation, methyl ester formation, Cbz protection, and hydrolysis of the sugars in good overall yield.[139–141]

Upon completion of this total synthesis, a solid-phase version was developed and a number of interesting analogues have since been designed, semisynthesized, and tested for biological activity. The solid-phase synthesis of vancomycin (**329**) followed similar lines to the strategy described above and is summarized in Scheme 55.[142a] A key factor in the success of this strategy was the use of a selenium-based safety-catch linker in which resin-bound selenoether **342** was cleaved with H_2O_2 to furnish allylester **343**, which was subsequently removed with nBu$_3$SnH and [Pd(PPh$_3$)$_4$]. Facilitated by these synthetic technologies, target-accelerated combinatorial synthesis of vancomycin back-to-back dimers led to the discovery of a number of highly potent antibiotics active against vancomycin-resistant enterococci. In this study, D-Ala-D-Ala-containing targets were utilized to induce rate accelerations in the olefin metathesis or disulfide bond formation to cause dimerization of monomeric vancomycin analogues.[142b]

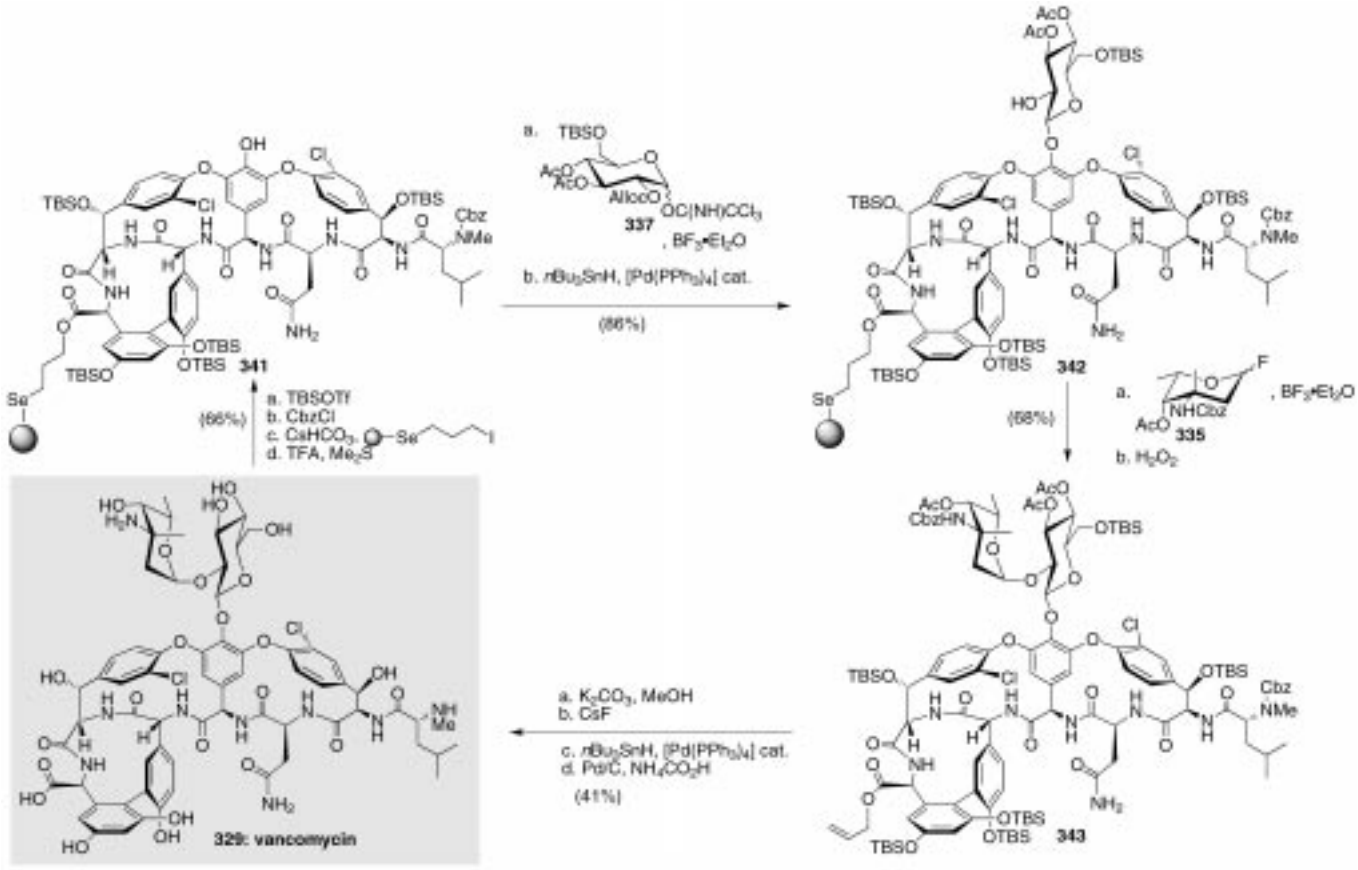
4.18. Everninomicin 13,384-1

Everninomicin 13,384-1 (Ziracin, **344**), a member of the orthosomicin class of antibiotics, represents a promising new weapon against drug-resistant bacteria including methicillin-resistant Staphylococci and vancomycin-resistant Streptococci and Enterococci. Isolated from *Micromonospora carbonacea var. africana* (found in a soil sample collected from the banks of the Nyiro River in Kenya), **344** possesses a complex oligosaccharide structure containing two sensitive orthoester moieties and terminating with two highly substituted aromatic esters. In addition, it hosts within its structure a 1,1′-disaccharide bridge, a nitrosugar (evernitrose), 13 rings, and 35 stereogenic centers.



344: everninomicin 13,384-1

Retrosynthetic analysis of **344** indicated that fluoride **375** (A_1B(A)C fragment, Scheme 57) and diol **394** (DEFGHA$_2$ fragment, Scheme 58) could be the penultimate building blocks for the intended construction. The larger fragment **394** was further disconnected at the EF glycosidic bond to unravel fragments **387** (DE, Scheme 58) and **383** (FGHA$_2$,

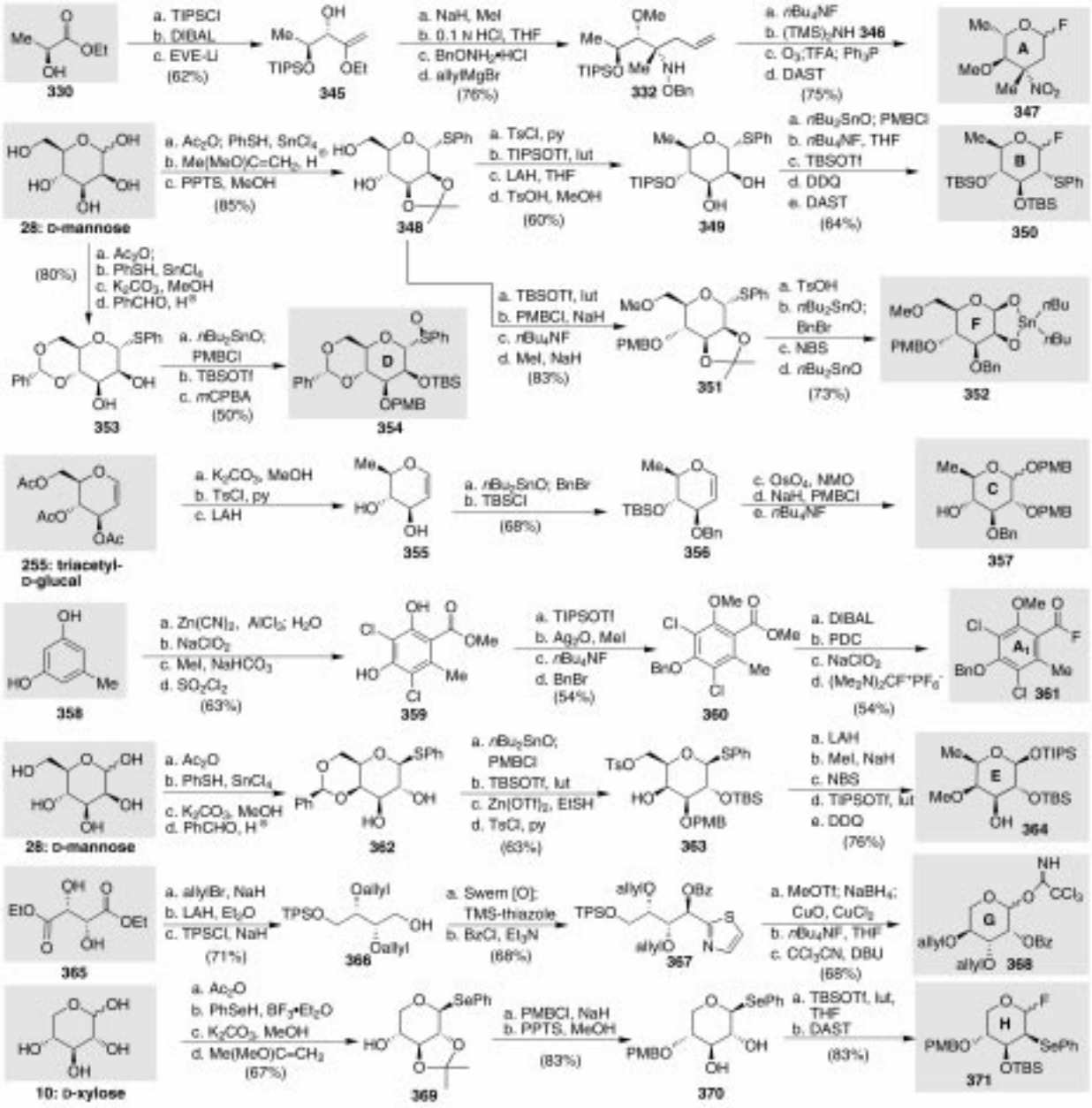


Scheme 55. Solid-phase semisynthesis of vancomycin (**329**) (2000).[142a]

Scheme 58) as potential key intermediates for its construction. Crucial to this total synthesis were 1,2-phenylseleno- and 1,2-phenylthio migrations, as described above in the methodologies section, that set the stage for the stereocontrolled syntheses of the CD and GH orthoesters and β-2-deoxyglycoside bond between rings B and C.

Scheme 56 summarizes the construction of the requisite building blocks **347**, **350**, **352**, **354**, **357**, **361**, **364**, **368**, and **371**. The construction of the evernitrose donor **347** involved an improved sequence along the lines of our original syntheses of both evernitrose and vancosamine.[139] Thus, methylation of alcohol **345** (derived from ethyl lactate (**330**)) with NaH/MeI, hydrolysis to the corresponding ketone with aqueous HCl, conversion into the oxime, and addition of allylmagnesium bromide furnished **332** (sse Scheme 54). Silyl group exchange (nBu$_4$NF; (TMS)$_2$NH (**346**), TMSCl) and ozonolysis, followed by sequential exposure to TFA and Ph$_3$P resulted in generation of the lactol, which was subsequently converted into glycosyl fluoride **347** upon treatment with DAST (75% overall yield). Building block B **350** was prepared by tosylation of the primary hydroxyl group of intermediate **348** (derived from D-mannose (**28**)), silylation, reduction with LAH, and acidic methanolysis of the acetonide group to afford diol **349**. Selective protections (nBu$_2$SnO/PMBCl, desilylation, resilylation, DDQ deprotection) and exposure to DAST caused the desired 1,2-migration of the thiophenyl group leading to the targeted glycosyl fluoride **350**.

Building block F **352** was synthesized from the readily available thioglycoside **348** as follows (Scheme 56). Selective silylation (TBSOTf/2,6-lutidine, 97%), PMB protection (NaH/PMBCl/nBu$_4$NI), desilylation, and methylation (NaH/MeI) furnished acetonide **351** in 83% overall yield. Acidic



Scheme 56. Synthesis of building blocks **347**, **350**, **357**, **354**, **364**, **352**, **368**, **371**, and **361** required for the total synthesis of everninomicin 13,384-1 (**344**) (1999).[143–146]

methanolysis (TsOH/MeOH), selective benzylation, and rupture of the phenylthio group with NBS/H_2O furnished the corresponding lactol, which was converted to the desired tin acetal **352** by exposure to nBu$_4$SnO in refluxing MeOH. Building block D was constructed from benzylidene **353** (derived from D-mannose (**28**)) by regioselective tin acetal mediated protection (nBu$_2$SnO/PMBCl/nBu$_4$NI), silylation (TBSOTf/2,6-lutidine), and oxidation of the sulfur group with mCPBA to afford the desired sulfoxide **354**. Building block C (**357**) was constructed in five steps from the readily available glucal **355**. Thus, tin acetal mediated benzylation of **355** (nBu$_2$SnO/BnBr/nBu$_4$NI) and silylation (TBSCl/imidazole) led to compound **356**. Hydroxylation (OsO_4/NMO), PMB protection (NaH/PMBCl/nBu$_4$NI), and exposure to nBu$_4$NF generated the desired building block **357** in 68 % overall yield.

The acyl fluoride **361** was formed from 5-methylresorcinol (**358**); a Gattermann reaction and core chlorination produced the fully substituted benzene ring. The synthesis of ring E **364** also began from D-mannose (**28**). PMB monoprotection of compound **362** (nBu$_2$SnO/PMBCl/nBu$_4$NI) and silylation (TBSOTf/2,6-lutidine), followed by cleavage of the benzylidene group (Zn(OTf)$_2$/EtSH) and selective tosylation of the primary hydroxyl group (TsCl/py), furnished **363**. LAH reduction, methylation (NaH/MeI), and cleavage of the phenylthio group (NBS/H_2O), followed by silylation (TIPSOTf/2,6-lutidine) and removal of the PMB group (DDQ), furnished the desired building block **364**.

Ring G trichloroacetimidate **368** was derived from diethyl-L-tartrate (**365**) by double allylation and reduction of both ester groups, followed by monosilylation to furnish hydroxy silyl ether **366**. Swern oxidation and exposure to TMS/thiazole afforded, after acidic workup (PPTS/MeOH) and benzoylation, the homologated chain **367**. Thiazole cleavage (MeOTf; $NaBH_4$; CuO; one-pot reaction) and desilylation (nBu$_4$NF) led to the lactol which was converted into the trichloroacetimidate **368**.

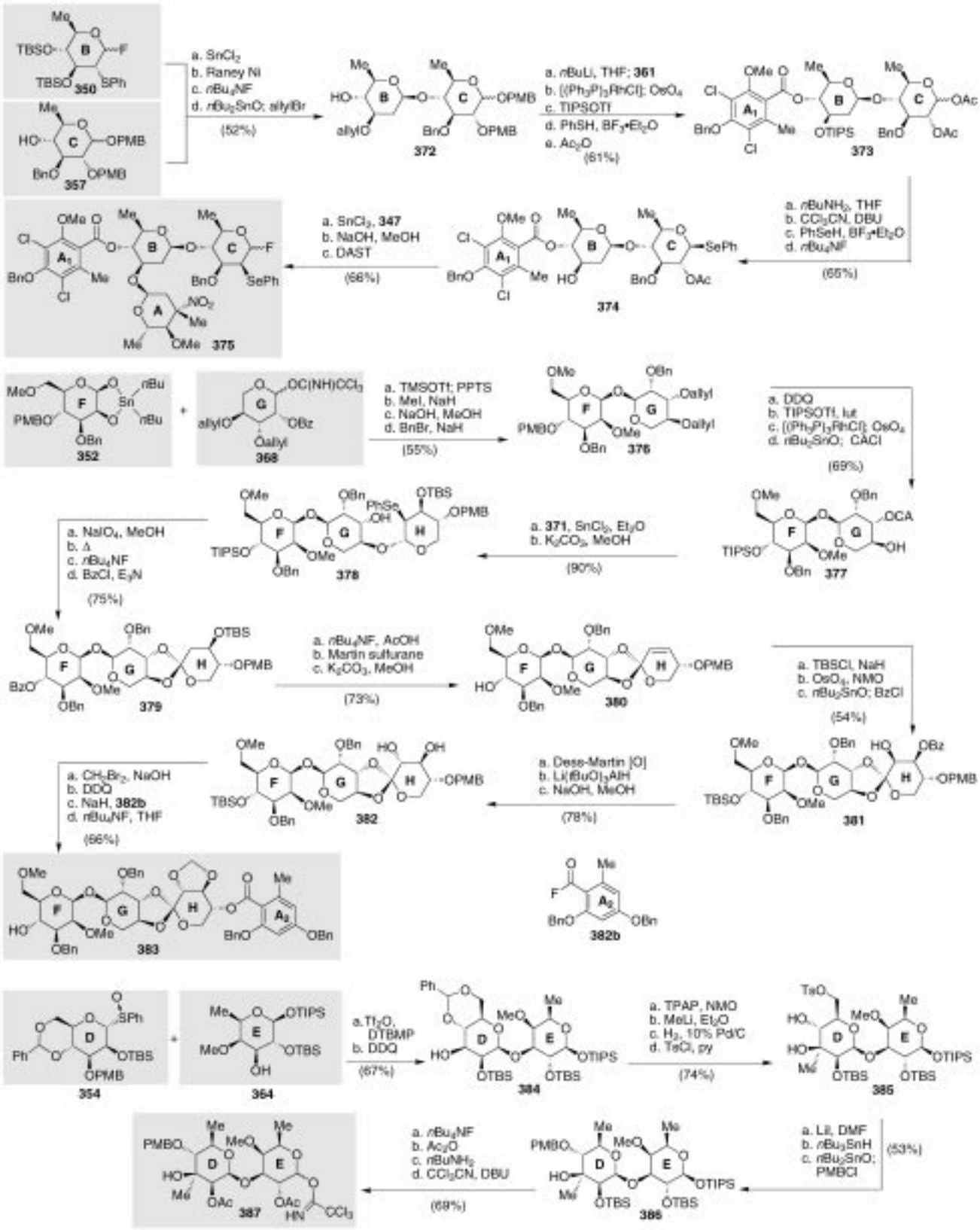
Building block H **371** was derived from D-xylose (**10**) as follows. Peracetylation of **10** (Ac_2O/Et_3N/4-DMAP), treatment with PhSeH/$BF_3\cdot Et_2O$, basic methanolysis (K_2CO_3/MeOH), and exposure to $CH_3(CH_3O)C{=}CH_2$/TFA furnished the 2,3-acetonide **369**. Protection (NaH/PMBCl/nBu$_4$NI, 95 % yield) and acetonide cleavage (PPTS/MeOH) then afforded diol **370**. The hydroxy group at the C3 position of the latter compound was selectively silylated, and then treatment with DAST funished the targeted 2-phenylselenoglycosyl fluoride **371**.

Scheme 57 shows the stereoselective coupling of building blocks **347**, **350**, **357**, and **361** to form the A$_1$B(A)C fragment **375**. Thus, $SnCl_2$-mediated coupling of glycosyl fluoride **350** with alcohol **357**, followed by reductive cleavage of the 2-thiophenyl group (Raney Ni), desilylation (nBu$_4$NF), and selective monoallylation (nBu$_2$SnO – allylbromide), furnished alcohol **372** in 52 % overall yield. Formation of the aromatic ester linking **372** and **361** mediated by nBuLi, followed by removal of the allyl group, silylation, PMB removal, and acetylation afforded diacetate **373**. Exposure of diacetate **373** to nBuNH$_2$ led to selective cleavage of the C1 acetate, and the liberated lactol was then converted into the β-phenylselenoglycoside via the trichloroacetimidate. Finally, removal of the TIPS group furnished A$_1$BC fragment **374**. Attachment of the evernitrose fragment **347** onto the A$_1$BC chain proceeded smoothly under the influence of $SnCl_2$, and basic hydrolysis of the acetate group led to the 2-hydroxy compound, whose treatment with DAST produced the targeted 2-phenylselenoglycosyl fluoride **375** in excellent yield and with inversion of stereochemistry at C2 of ring C.

The assembly of building blocks **352**, **368**, and **371** to form the targeted FGHA$_2$ intermediate **383** required the use of the new technology for the construction of 1,1′-disaccharides (Scheme 25). The coupling of tin acetal **352** with trichloroacetimidate **368** proceeded smoothly under the catalytic influence of TMSOTf in CH_2Cl_2 and led, after PPTS-induced cleavage of the intermediate TMS ether, to the desired 1,1′-disaccharide linkage. Methylation, debenzoylation, and benzylation afforded disaccharide **376**. The PMB group of ring F was replaced with a TIPS group (DDQ, 91 % yield; TIPSOTf/2,6-lutidine, 97 % yield) and removal of the allyl protecting groups was followed by tin acetal mediated chloroacetylation to furnish **377**. Coupling of **377** with glycosyl fluoride **371** ($SnCl_2$, Et_2O) proceeded smoothly to give stereoselectively, and following deacetylation, trisaccharide **378**.

Trisaccharide **378** was now poised for a Sinaÿ orthoester formation. Thus, oxidation of the phenylseleno group with $NaIO_4$, followed by heating of the crude selenoxide in a mixture of vinyl acetate, toluene, and diisopropylamine (2:2:1) in a sealed tube at 140 °C, effected sequential *syn* elimination (*syn* towards the anomeric position) and ring closure, furnishing the orthoester in 81 % yield and with approximately 8:1 diastereoselectivity. Exchange of protecting groups and subsequent dehydration with Martin sulfurane eventually led to olefin **380**, which was set for a dihydroxylation reaction. Treatment of the highly sensitive olefinic orthoester with NMO/OsO_4 in the presence of quinuclidine led to a *cis*-1,2-diol, which was then regioselectively converted into the monobenzoate **381** by treatment with nBu$_2$SnO/BzCl. Oxidation (Dess – Martin periodinane) and reduction with Li(tBuO)$_3$AlH inverted the configuration at the C2 position of the H ring and, following debenzoylation, afforded *trans* diol **382**. Transformation of the resulting *trans*-1,2 diol system into the desired methylene acetal functionality was achieved by slowly adding it to a mixture of aqueous NaOH, CH_2Br_2, and nBu$_4$NBr at 65 °C. The remaining steps for the completion of the synthesis of **383** involved DDQ-induced removal of the PMB group, esterification of the resulting compound with the acyl fluoride **382b**, and removal of the TBS group from ring F.

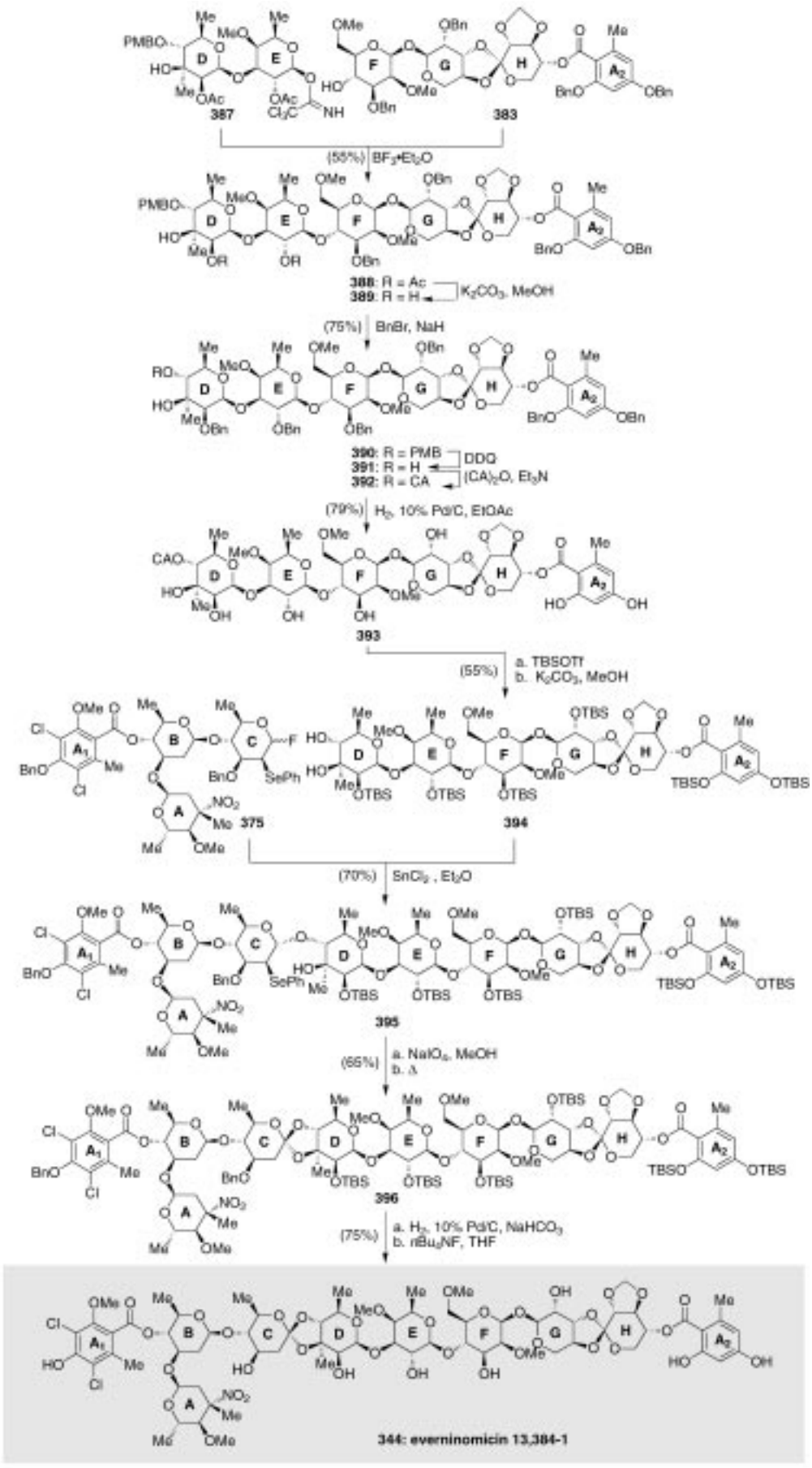
The construction of key intermediate **387** from fragments **354** and **364** was achieved by the Kahne sulfoxide glycosidation technology (Scheme 57). Thus, stereoselective coupling of sulfoxide **354** with acceptor **364** proceeded in the presence of Tf_2O and DTBMP, to afford the β-mannoside in 71 % yield. Removal of the PMB group (DDQ, 95 %), oxidation to the corresponding ketone (TPAP/NMO), and exposure of the latter compound to MeLi in Et_2O produced the desired tertiary alcohol in high overall yield. The benzylidene group was removed by hydrogenolysis (97 % yield) and the primary hydroxyl group was selectively tosylated to afford **385**. Replacement of the tosylate with an iodide, reduction with



Scheme 57. Synthesis of the $A_1B(A)C$, DE, and $FGHA_2$ fragments (**375**, **387**, and **383**, respectively) of everninomicin 13,384–1 (**344**) (1999).[143–146]

*n*BuSnH/AIBN, and PMB protection led to **386**. Desilylation and peracetylation was followed by removal of the anomeric acetate and conversion into the trichloroacetimidate to afford **387**.

The coupling of the key intermediates **387** and **383** and the elaboration of the resulting fragment to the next advanced key intermediate, **394**, is shown in Scheme 58. Thus, reaction of the trichloroacetimidate **387** with fragment **383** furnished

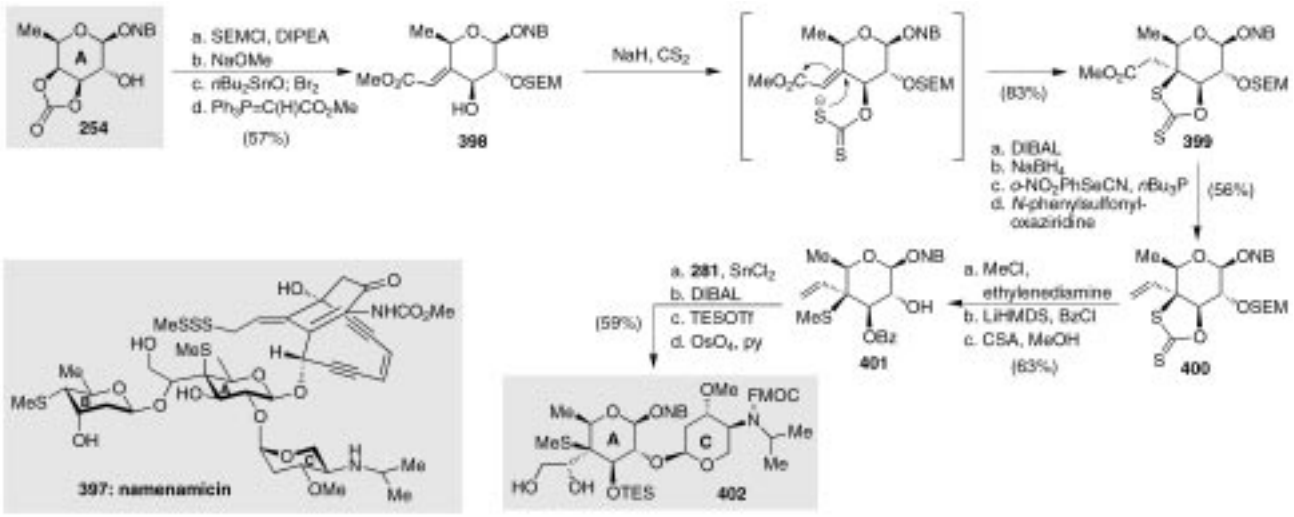


Scheme 58. Completion of the total synthesis of everninomicin 13,384-1 (**344**) (1999).[143–146]

oligosaccharide **388** with the desired β-glycoside configuration (between rings E and F). Several subsequent protecting group exchanges afforded DEFGHA_2 fragment **394**, ready for the next coupling. Coupling of the A_1B(A)C glycosyl fluoride donor **375** with **394** proceeded smoothly and with complete stereocontrol to afford the 2-phenylselenoglycoside **395**. Formation of the remaining orthoester site was then accomplished with equal facility under the Sinaÿ conditions to afford the fully protected everninomicin 13,384-1 derivative **396** as a single isomer. Generation of everninomicin 13,384-1 (**344**) from **396** entailed hydrogenolysis (H_2, Pd/C, $NaHCO_3$, *t*BuOMe) and desilylation (*n*Bu_4NF, THF) leading to **344**. As a result of this synthesis,[143–146] the stage is now set for further advances in the antibiotics field, including semisynthesis of designed analogues, solid-phase synthesis, and chemical biology studies.

4.19. Namenamicin Carbohydrate Domain

Namenamicin (**397**, Scheme 59), recently isolated from an ascidian (*Polysyncraton lithostrontum*), is notably the only enediyne natural product of marine origin. Although its trisaccharide domain is reminiscent of esperamicin A_1, it contains an unprecedented and unusual linkage between rings A and B. Beginning with the same ring A intermediate (**254**) used in the calicheamicin synthesis (see Scheme 46), a cyclic xanthate based approach to the ring A thioether was initiated. Thus, **254** was trans-

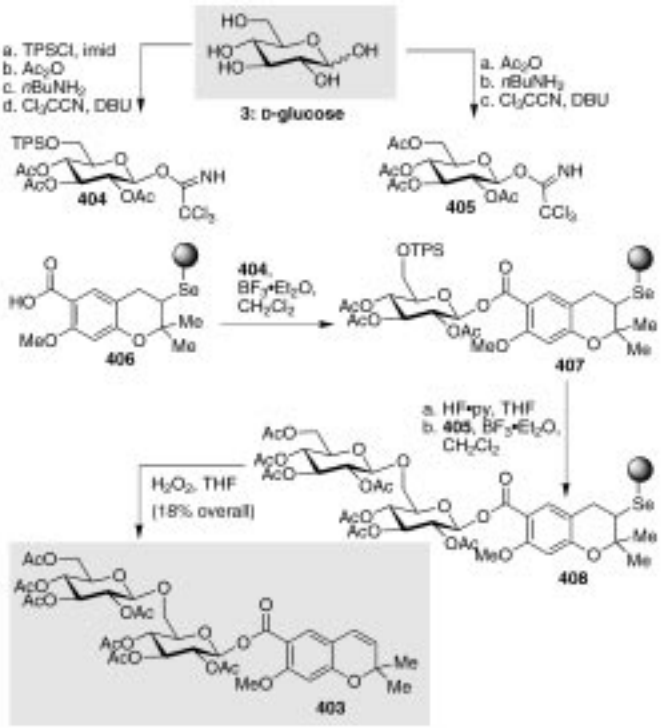


Scheme 59. Synthesis of namenamicin A – C disaccharide **402** (1999).[147]

formed into olefin **398** in four steps. Treatment of **398** with NaH and CS_2 afforded cyclic xanthate **399**. Subsequent exchange of protecting groups and elimination, followed by coupling with fluoride **281** (see Scheme 47) and dihydroxylation, furnished diol **402**.[147]

4.20. Macrophylloside D Heptaacetate

In defining the versatility of a selenium-linking strategy for the solid-phase synthesis of benzopyran-containing natural products and related compounds, the synthesis of macrophylloside D heptaacetate (**403**, Scheme 60),[148, 149] a derivative of a chromene glycoside isolated from *Gentiana macrophylla*, was developed from resin-bound selenoether **406**. The requisite trichloroacetimidate donors **404** and **405** were obtained by standard chemistry from D-glucose (**3**). Carboxylic acid resin **406** was treated with trichloroacetimidate **404** in the presence of $BF_3 \cdot Et_2O$ to smoothly furnish ester **407** in 91% yield. Selective deprotection with HF · py (89%) followed by a second coupling between the resin-bound monosaccharide and trichloroacetimidate **405** under similar conditions afforded **408** as a single anomer and in 57% yield. Finally, the disaccharide was cleaved from the resin (H_2O_2, THF) to afford heptaacetylated macrophylloside **403** in 18% overall yield based on **406**.

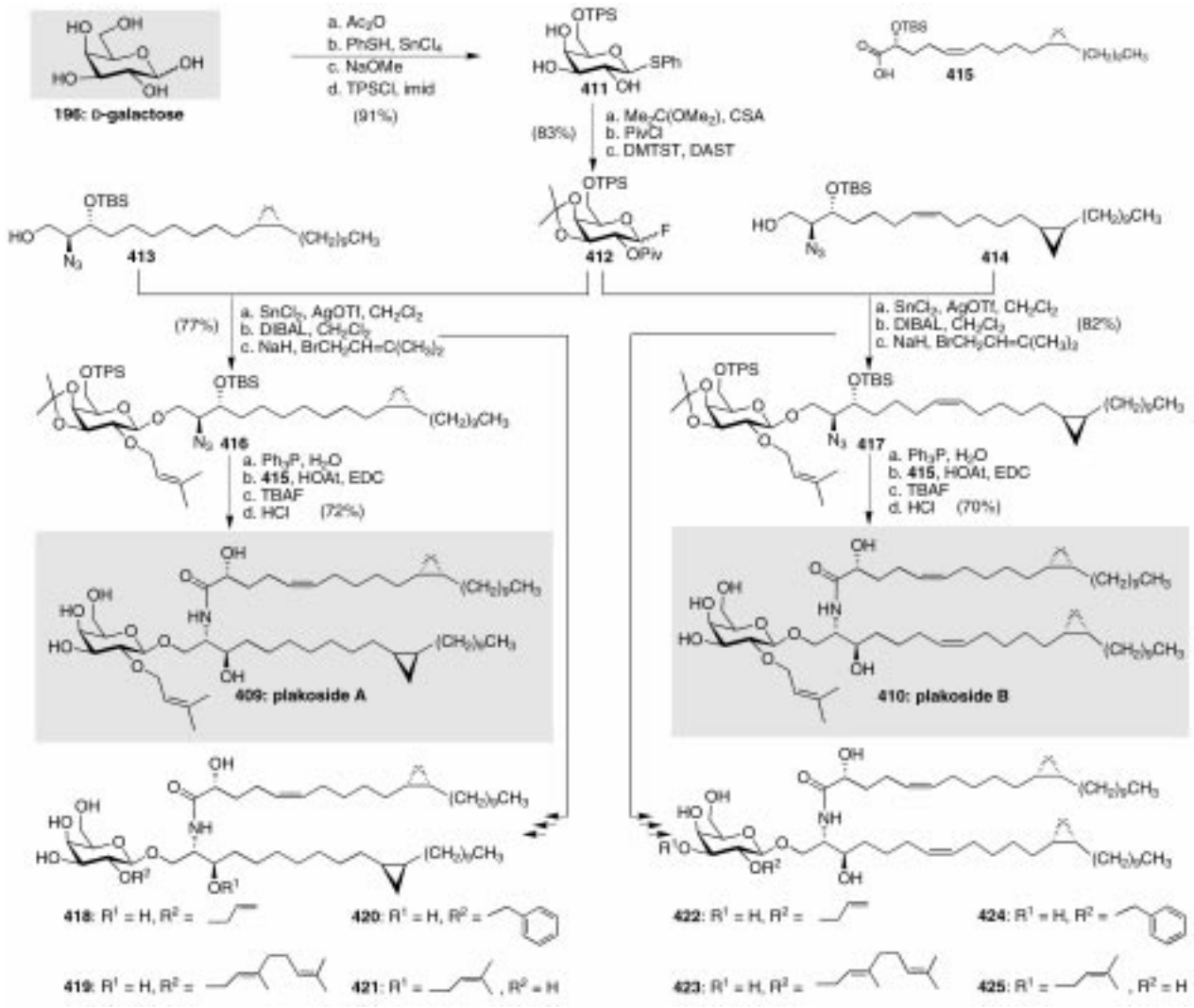


Scheme 60. Solid-phase synthesis of peracetyl macrophylloside D (**403**) from D-glucose (**3**) (2000).[148, 149]

4.21. Plakosides A and B

Plakosides A (**409**) and B (**410**) (Scheme 61), recently isolated from the marine sponges *Plakortis simplex*, are potent immunosuppressive agents and contain interesting functionalities not common to other glycosphingolipids. Among these features are a cyclopropane ring on their sphingosine chain and a prenyloxy group on the C2 position of the carbohydrate moiety, which makes them interesting candidates for total synthesis, library construction, and chemical biology studies. The total synthesis of these target molecules, recently developed in our laboratories, is summarized in Scheme 61.[150] Thus, galactosyl fluoride **412**, obtained from D-galactose (**196**) in seven steps, was coupled with azidosphingosine **413** to afford the expected β-glycoside in 93% yield. DIBAL cleavage of the pivalate ester was followed by installation of the prenyloxy group at the C2 position to afford **416**. Completion of the synthesis required reduction of the azide group, coupling with carboxylic acid **415**, and removal of the protecting groups to afford plakoside A (**409**) in high overall yield.

Plakoside B (**410**) and several designed analogues (such as **418** – **425**) were constructed by similar methods (Scheme 61). The biological activities of plakosides A and B and their analogues were evaluated in collaboration with a research



Scheme 61. Total synthesis of plakosides A (**409**) and B (**410**), and analogues thereof (2000).[150]

group at Novartis[150] to provide information about immunosuppressive activity (MLR and Con A response) and potential cytotoxic and cytostatic effects (bone marrow cell proliferation). The IC_{50} values of the plakosides and several analogues synthesized in this program in comparison to reference compounds are provided in Table 9.

Table 9. Inhibitory effects of plakosides A (**409**) and B (**410**), their analogues **418**–**425**, and two reference compounds (Tests: MLR, the Con A response, and the bone marrow cell proliferation assays).[150]

Compound	IC_{50} [μM] MLR	Con A response	Bone marrow cell proliferation
cyclosporin A	0.014	0.14	> 1
azathioprine	0.028	0.15	0.050
409	> 50	> 50	50
410	> 50	> 50	> 50
418	7.1	30	3.3
419	28	> 50	18
420	> 50	> 50	> 50
421	28	30	24
422	> 50	> 50	40
423	> 50	> 50	> 50
424	> 50	> 50	50
425	> 50	> 50	29

5. Design and Synthesis of Novel Carbohydrates for Chemical Biology Studies

One of our strongest motivations for developing carbohydrate-based enabling technologies was to facilitate studies in biology and medicine. Thus, we have utilized the developed chemistry in the construction of combinatorial libraries for chemical biology investigations and structure-activity relationship studies in several instances, including with vancomycin, the plakosides, and the benzopyran-type structures discussed above. Another field of investigation, that of DNA-binding molecules, was inspired by the mode of action of calicheamicin γ_1^I. Yet another endeavor was initiated to capitalize on the structure and functionality of the carbohydrate ring framework as a scaffold upon which to design and build peptide and carbohydrate mimetics. Finally, a series of designed oligosaccharides with potential in biology were synthesized that exploited both solution- and solid-phase synthetic technologies. In the following section we will highlight a number of such investigations.

5.1. DNA-Binding Oligosaccharides

The observation that the calicheamicin γ_1^I oligosaccharide binds to certain DNA sequences (in particular TCCT, TCTC, and TTTT) with considerable selectivity, and knowledge of the importance in biology and medicine of sequence-specific small molecules that bind to DNA, prompted us to initiate a program aimed at the design, chemical synthesis, and study of a number of calicheamicin γ_1^I oligosaccharide analogues. In order to study the effect of the iodine atom on the binding properties of calicheamicin's oligosaccharide to DNA, a series of ring C analogues (R = Me, H, F, Cl, or Br, see structure **426**) were synthesized by applying the chemistry developed during the total synthesis of the natural product (see Scheme 46). The results of the binding studies with these synthetic molecules revealed the importance of the iodide residue in conferring high affinity ($I \approx Br > Cl > Me > F > H$) to the molecule (Table 10).[126] These molecules were also used in NMR studies to define the precise mode of binding of the oligosaccharide to DNA's minor groove.[123, 124]

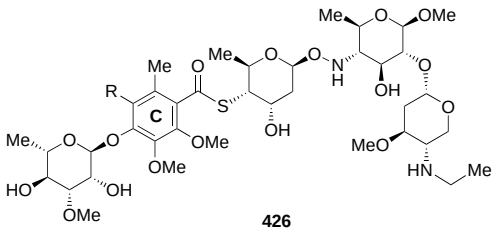


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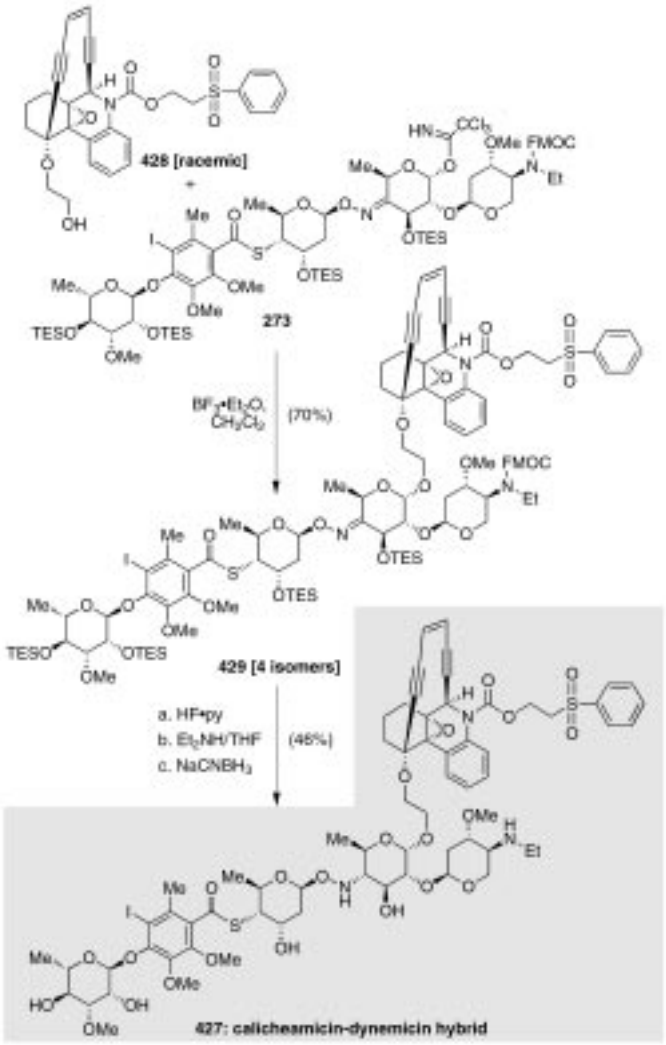
Table 10. Binding affinity of calicheamicin γ_1^I and various analogues of the calicheamicin oligosaccharide at a single TCCT – AGGA site within duplex DNA.

Ligand	K_{obs}[a] [μM]	ΔG[b] [kcal mol^{-1}]	$\Delta\Delta G$[c] [kcal mol^{-1}]
calicheamicin γ_1^I (**251**)	0.135 ± 0.006	– 9.7	–
I sugar **426a**	4.1 ± 0.4	– 7.6	2.1
Br sugar **426b**	10.0 ± 1.7	– 7.1	2.6
Cl sugar **426c**	32.0 ± 3.3	– 6.4	3.3
F sugar **426d**	44.0 ± 3.1	– 6.2	3.5
Me sugar **426e**	38.0 ± 5.0	– 6.3	3.4
H sugar **426f**	180.0 ± 19.0	– 5.3	4.4

[a] K_{obs} is the apparent dissociation constant of either calicheamicin (K_D) or the calicheamicin oligosaccharide (K_I). [b] $\Delta G = RT \ln K_{obs}$; $T = 310.15$ K. [c] $\Delta\Delta G$ is ΔG for the oligosaccharide relative to ΔG for intact calicheamicin γ_1^I.[126]

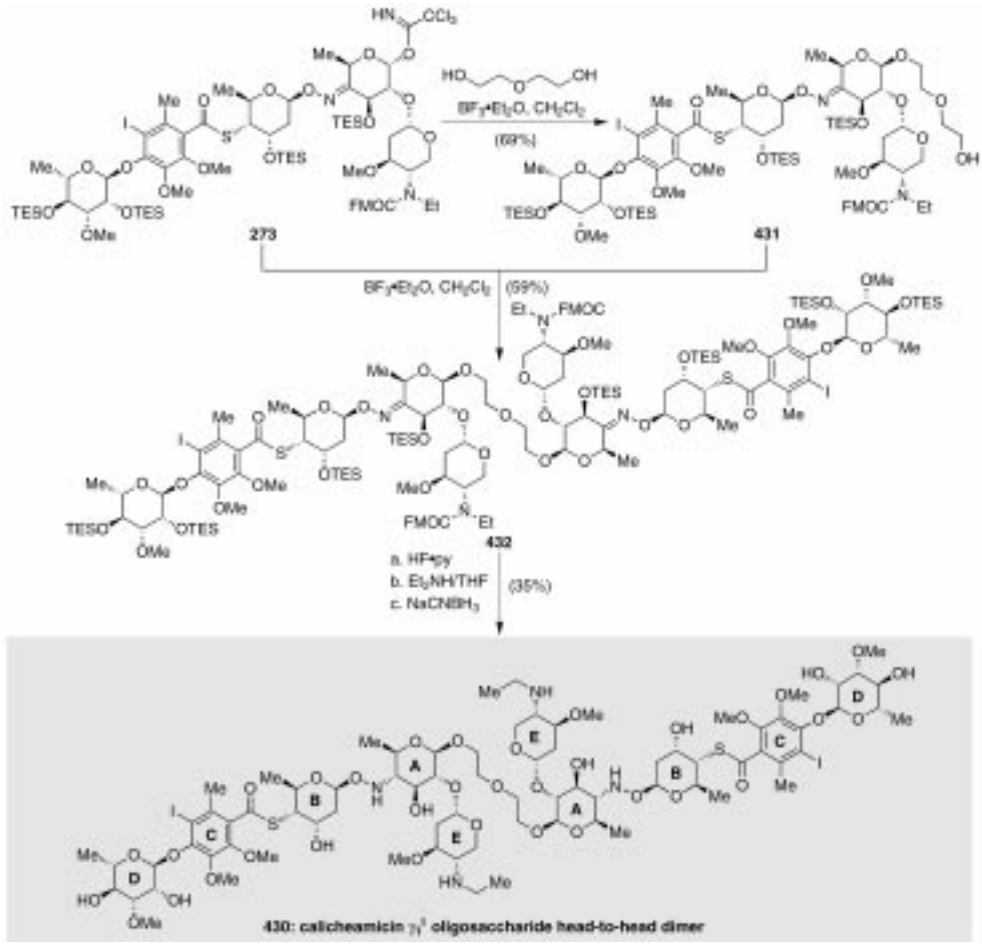
In an effort to prepare totally designed DNA-cleaving molecules with sequence selectivity, we attempted to merge the chemistry of calicheamicin γ_1^I with that of dynemicin, another novel enediyne antibiotic.[151, 152] Thus, synthetic DNA-cleaving molecule **428** (Scheme 62), which was designed based on the structure and mechanism of action of dynemicin, was coupled with the calicheamicin oligosaccharide trichloroacetimidate **273** in the presence of $BF_3 \cdot Et_2O$ to produce conjugate **429** as an anomeric mixture. The α-anomer **429** (shown) was then converted into the targeted calicheamicin – dynemicin hybrid **427** whose DNA-cleaving properties were studied. Interestingly, neither the potency nor its



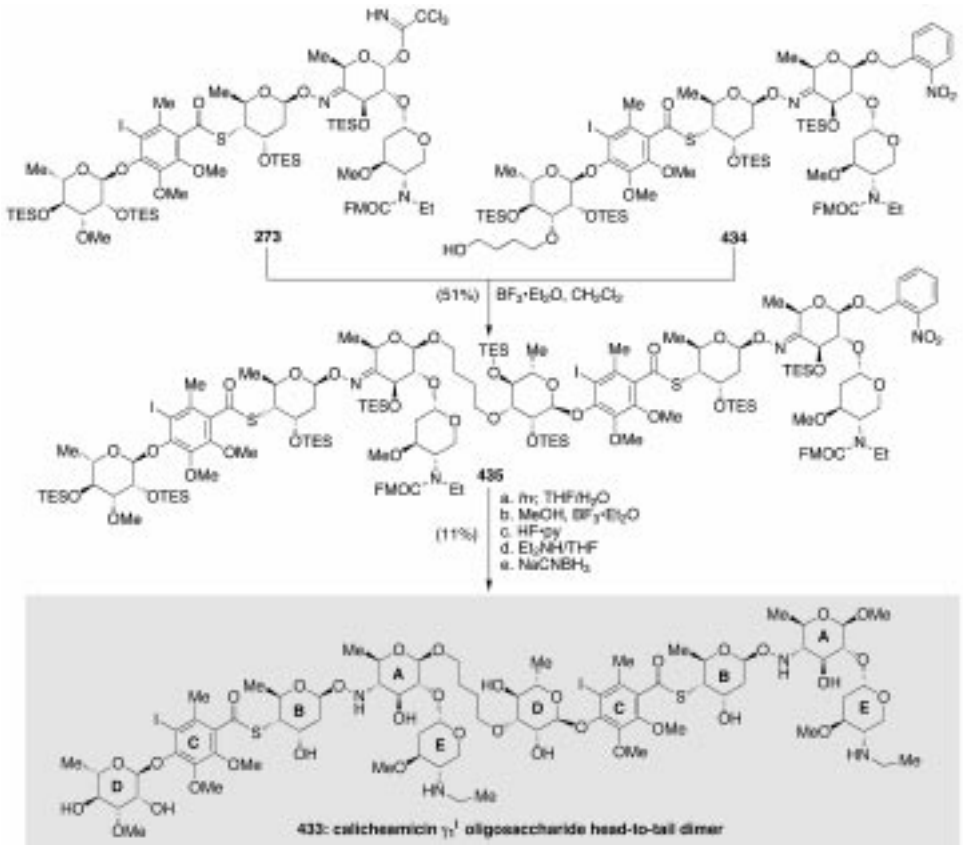
Scheme 62. Synthesis of calicheamicin – dynemicin hybrid **427** (1992).[151, 152] (Only one diastereoisomer, of the four prepared, is shown.)

selectivity matched those of calicheamicin γ_1^I. This underscores the importance of precisely fitting the "molecular warhead" domain of the molecule within its receptor for optimal activity.

In another study within this area, and following NMR and computer modeling studies, both the head-to-head (Scheme 63) and the head-to-tail (Scheme 64) dimers (**430** and **433**, respectively) were designed and synthesized with the appropriate length tethers. For the synthesis of the head-to-head dimer **430** (Scheme 63), one equivalent of the oligosaccharide trichloroacetimidate **273** was reacted with diethylene glycol in the presence of $BF_3 \cdot Et_2O$ to furnish the desired β-anomer, which was subsequently reacted with a second equivalent of the oligosaccharide trichloroacetimidate **273** under the $BF_3 \cdot Et_2O$ conditions to afford the desired dimer **432**. Global deprotections, followed by reduction of the oxime with sodium cyanoborohydride in the presence of Lewis acid, led to the targeted, head-to-head dimer **430**. The head-to-tail dimer **433**, which has the potential of growth to higher homologues, was synthesized as shown in Scheme 64. Thus, compound **434** with the optimum size and point of attachment



Scheme 63. Synthesis of the calicheamicin γ_1^I oligosaccharide head-to-head dimer **430** (1995).[153–158]



Scheme 64. Synthesis of calicheamicin γ_1^I oligosaccharide head-to-tail dimer **433** (1996).[153–158]

of the tether, was constructed using standard chemistry and then glycosidated with trichloroacetimidate **273** in the presence of $BF_3 \cdot Et_2O$, to furnish dimer **435**. Further manipulations including photolytic cleavage of the anomeric nitrobenzyl ether, methyl glycoside formation, deprotection, and reduction of the oxime provided the targeted, head-to-tail dimer **433**.[153, 154]

Both dimers **430** and **433** exhibited interesting DNA-interacting properties, by binding selectively to TCCT-rich sites with an affinity approximately 1000 times higher than the monomeric oligosaccharide. Figures 5 and 6 depict autoradiodiagrams of the gels showing products of calicheamicin-induced DNA cleavage in the presence of the monomeric and dimeric synthetic calicheamicin oligosaccharides. Figure 7 illustrates the proposed mode of binding of monomeric and dimeric oligosaccharides to the minor groove of duplex DNA based on molecular modeling.[153–158]

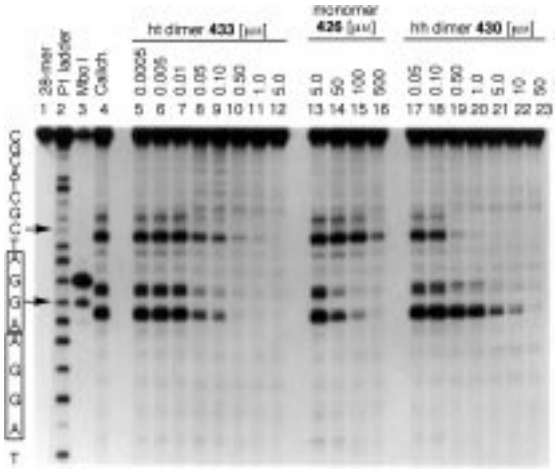


Figure 5. Autoradiodiagram of denaturing polyacrylamide gel showing products of calicheamicin-induced DNA cleavage of a [5′-^{32}P]-labeled AGGAAGGA-containing DNA duplex in the presence of oligosaccharides **426a** (monomer), **430** (head-to-head dimer, hh dimer), or **433** (head-to-tail dimer, ht dimer). Lane 1: 28-mer. Lane 2: 28-mer ladder resulting from partial digestion with nuclease P1. Lane 3: marker lane containing the products of DNA digestion with *Mbo*I restriction enzyme. Lane 4: products of DNA cleavage with calicheamicin (2.5 μM). Lanes 5–23: products of DNA cleavage with calicheamicin (2.5 μM) in the presence of head-to-tail dimer **433** (lanes 5–12), monomer **426a** (lanes 13–16), and head-to-head dimer **430** (lanes 17–23). Reproduced with permission from ref. [154].

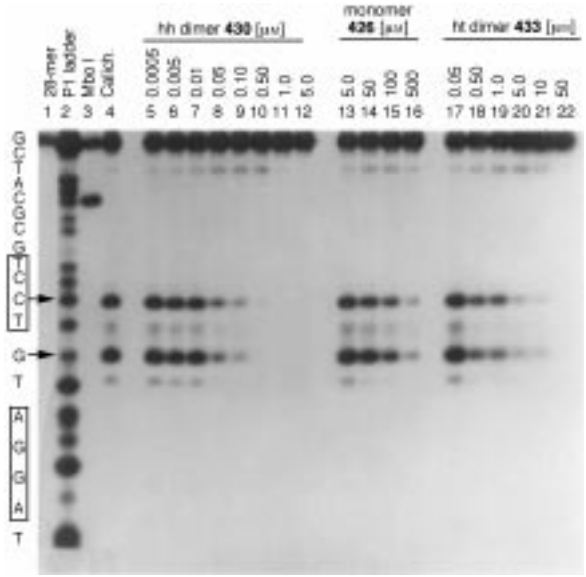


Figure 6. Autoradiodiagram of denaturing polyacrylamide gel showing products of calicheamicin-induced DNA cleavage of [5′-^{32}P]-labeled CGTAGCCGTAGGATG–TCCTGCGCATGCG DNA duplex in the presence of oligosaccharides **426a** (monomer), **430** (head-to-head dimer, hh dimer), and **433** (head-to-tail dimer, ht dimer). Lane 1: 28-mer. Lane 2: 28-mer ladder resulting from partial digestion with nuclease P1. Lane 3: marker lane containing the products of DNA digestion with *Hha*I restriction enzyme. Lane 4: products of DNA cleavage with calicheamicin (2.5 μM). Lanes 5–22: products of DNA cleavage with calicheamicin (2.5 μM) in the presence of dimer **430** (lanes 5–12), monomer **426a** (lanes 13–16), and dimer **433** (lanes 17–22). Reproduced with permission from ref. [154].

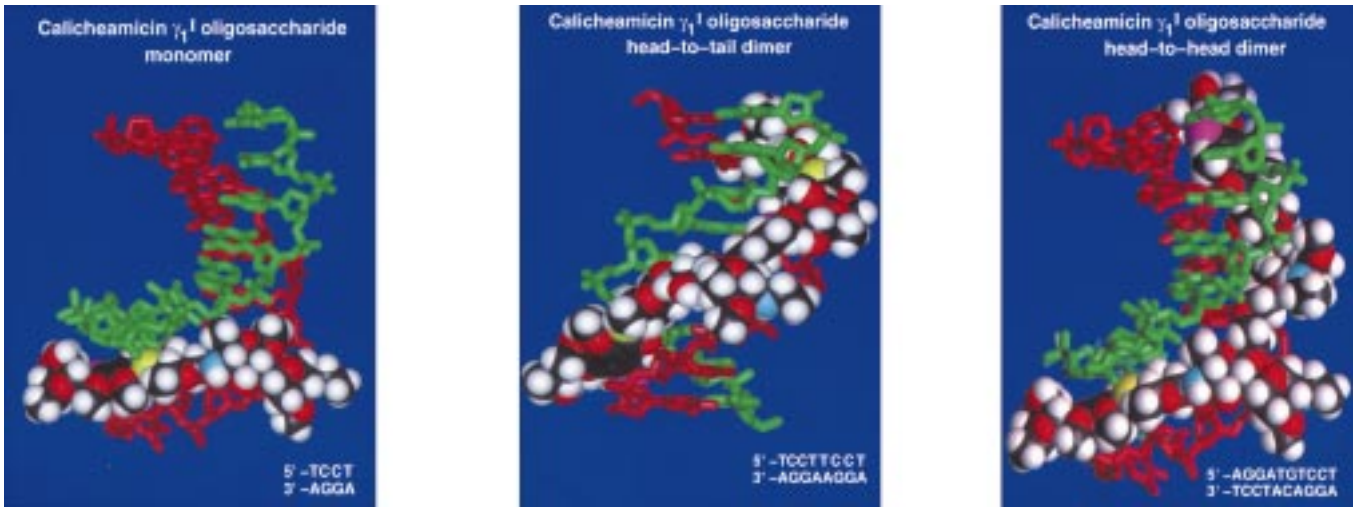
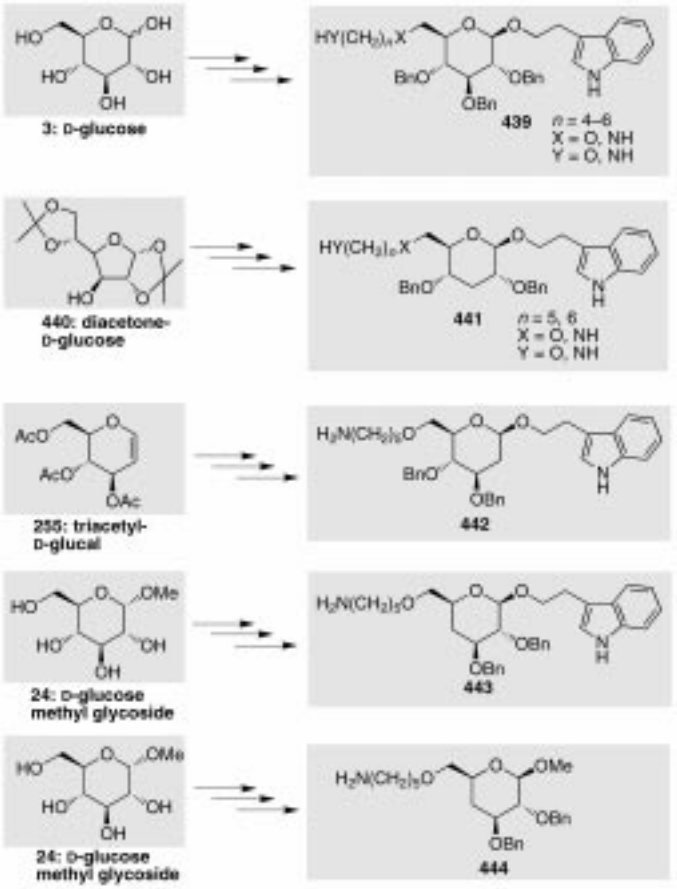


Figure 7. Computer-generated molecular models of oligosaccharide–DNA complexes. Left: monomer **426a** bound to 5′-TCCT–AGGA-3′. Center: head-to-tail dimer **433** bound to 5′-TCCTTCCT–AGGAAGGA-3′. Right: head-to-head dimer **430** bound to 5′-AGGATGTCCT–AGGACATCCT-3′. The DNA strands are displayed in green and red. Color code for the oligosaccharide atoms: C black, H white, O red, N blue, S yellow, I purple. Modeling studies and interactive docking were done on a SGI Indigo-2 workstation with Insight II (Biosym Technologies, Inc., San Diego, CA). Pictures were created using AVS (AVS Inc., Waltham, MA) and locally developed modules on a DEC Alpha 3000/500 computer with a Kubota Pacific Denali graphics card. Reproduced with permission from ref. [154].

5.2. Carbohydrate-Based Peptidomimetics

In 1988, and in collaboration with Hirschman and Smith at the University of Pennsylvania, we initiated a research program based on the concept of utilizing carbohydrate frameworks as templates for the design and synthesis of peptide mimetics.[159, 160] This principle was originally demonstrated with the design, synthesis, and biological investigation of glucose-based somatostatin analogues (**439** and **441**–**444**, Scheme 65). Inspection of these structures and comparison



Scheme 65. Synthesis of carbohydrate-based peptidomimetics (1992, with Hirschmann and Smith).[159, 160]

with those of somatostatin (**436**) and the previously synthesized cyclic hexapeptides **437** and MK-678 (**438**) reveal their resemblance to the parent compounds in that they retain critical amino acid side chains in the proper spatial orientation; yet they differ from them in that they are devoid of both the peptide backbone and the metabolically fragile amide bonds. Based on molecular modeling and NMR studies, the analogues shown in Scheme 65 and others like them were designed. Their chemical syntheses proceeded smoothly from the indicated starting materials by standard chemistry. Biological evaluation of the synthetic materials revealed μM binding affinities to the peptide hormone somatostatin receptor (SRIF) in a dose-dependent manner (see Table 11). This first report sparked several other related studies in which

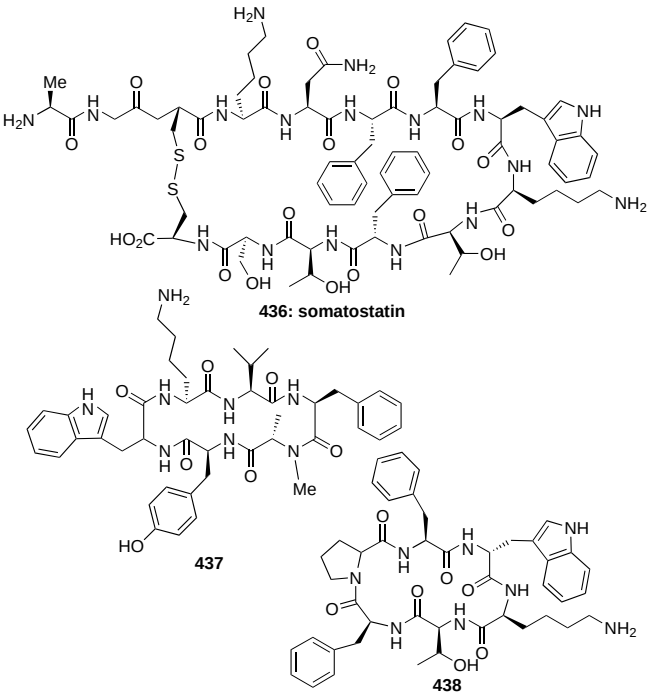


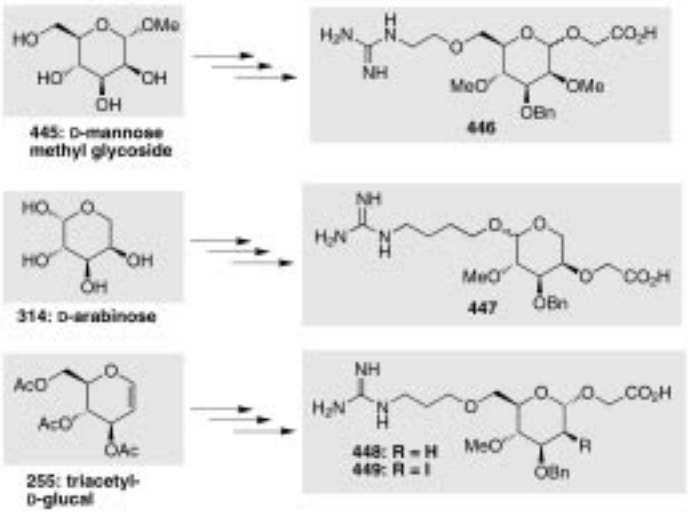
Table 11. In vitro SRIF binding affinities of selected peptides and peptidomimetics.[159, 160]

Compound			IC_{50}[a] [μM]	
Peptide				
somatostatin (**436**)			0.00083	
437			NT	
MK-678 (**438**)			0.0023	
Sugar peptidomimetics			IC_{50} [μM]	
O-linked	N-linked	*n*	O-linked	N-linked
439a	**439e**	5	15.0	14.0
439b	**439f**	4	NT	NT
439c	**439g**	6	11.0	5.1
441a	**441c**	5	8.4	10.0
441b	**441d**	6	6.6	34.0
442		5	35.0	
443		5	47.0	

[a] ^{125}-I-Tyr^{11}-SRFI; NT: Lower affinity than that of **439e** at a concentration of 2×10^{-5} M; dose response curve not obtained.

carbohydrate templates were utilized to construct peptide mimetics and other related molecules.[161]

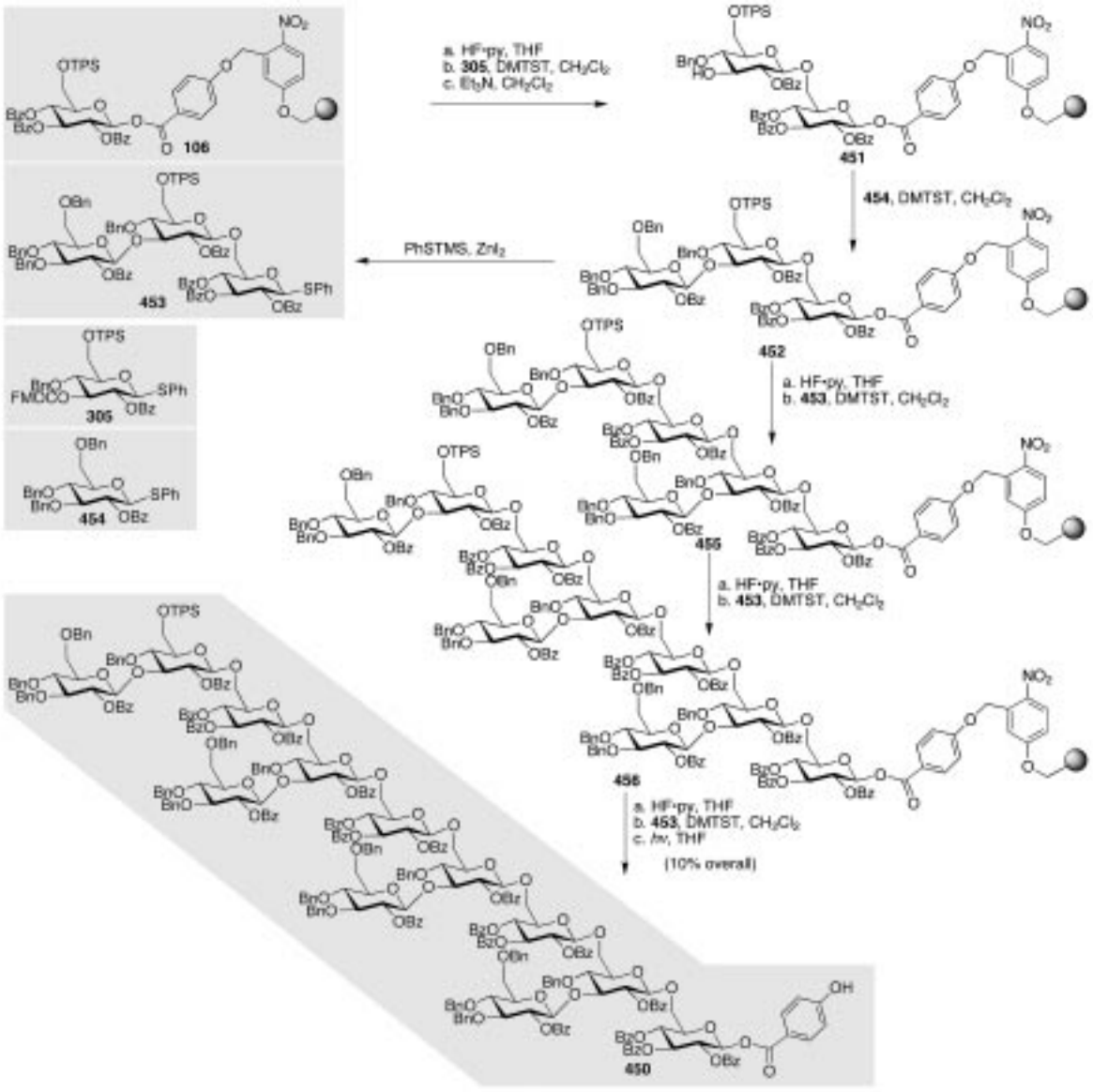
In a recent example from our laboratories at the Scripps Research Institute, a library of carbohydrate-based peptide mimetics of cRGD*F*V (a cyclic peptide which is a known antagonist of integrin $\alpha_V\beta_3$) was designed, synthesized, and screened in search of angiogenesis inhibitors.[162] A number of these compounds **446**–**449**, together with summaries of their syntheses, are shown in Scheme 66. The compounds were prepared from D-mannose methylglycoside (**445**), D-arabinose (**314**), and triacetoxy-D-glucal (**255**). Preliminary biological data indicated that, unlike **439a** (Scheme 65 and Table 11), these compounds do not bind to integrin $\alpha_V\beta_3$. Compounds **446**–**449** were also tested in other cell adhesion assays against the integrin $\alpha_{IIb}\beta_3$, and compound **449** showed a weak inhibition of cell adhesion mediated by $\alpha_{IIb}\beta_3$ (IC_{50} value: 85 μM).



Scheme 66. Synthesis of carbohydrate-based mimetics of cRGDTV (1997).[162]

5.3. Large Oligosaccharides

In a rather daring venture, the modified photolabile linking strategy described above (Scheme 27) was applied to the synthesis of the branched dodecasaccharide **450** (Scheme 67), which represents one of the largest oligosaccharides to be synthesized on solid phase.[88] Thus, resin-bound trisaccharide **452** was constructed from resin-bound monosaccharide **106** (Scheme 27) and monosaccharides **305** and **454**. This trisaccharide resin **452** was then cleaved releasing the subsequently used building block trisaccharide **453**. Following removal of the silyl group from resin **452**, treatment with **453** in the presence of DMTST furnished hexasaccharide-conjugate **455**. Reiteration of the process (desilylation and coupling with trisaccharide **453**) led to nonasaccharide **456** and the corresponding dodecasaccharide conjugates. Photolytic cleavage from the resin furnished the targeted dodecasaccharide **450**. The advantages of this method include high convergence, high yielding glycosidation steps, and maintenance of anomeric



Scheme 67. Solid-phase synthesis of model dodecasaccharide **450** (1998).[88]

integrity during the loading and unloading steps, which make the method applicable to larger and more diverse carbohydrate systems as well as amenable to automation.

6. Summary and Outlook

The blend of carbohydrate chemistry described within this article has been a source of enormous satisfaction and reward for all of us involved in it. It would not have been possible without the pioneering works of those who dedicated their careers to this important field of chemistry and who gave us the framework and the tools to shape our own research, which was primarily directed at the chemical synthesis and chemical biology of natural and designed molecules. If in the process of borrowing chemistry from the carbohydrate chemists, we have contributed some novelty back to the field, we feel fortunate and blessed. It is our hope that, through this review, the reader will benefit by realizing the awesome power of carbohydrate chemistry in providing enabling technologies for delivering highly complex molecules and facilitating chemical biology and drug discovery endeavors.

Despite the great strides, however, there still remain gaps in our ability to fully control the stereochemistry of the glycosidation process, as well as to make it, in general, as efficient as its peptide and phosphate bond forming counterparts. Solutions for such gaps are needed before we can truly enjoy the widespread and rapid construction of any given oligosaccharide at will, either by solution- or solid-phase methods. Automation will then become routine and will further facilitate both chemical and biological investigations. Indeed, as the human genome is fully deciphered, it will be up to such major breakthroughs in chemistry, with combinatorial synthesis of small organic molecule libraries, to confront the drug discovery process through identification, validation, and modulation of disease relevant targets.

Abbreviations

Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	2,2′-azobisisobutyronitrile
alloc	allyloxycarbonyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluoride
Bz	benzoyl
CA	chloroacetyl
CAN	cerium ammonium nitrate
Cbz	benzyloxycarbonyl
CMPI	*N*-methyl-2-chloropyridinium iodide
col	2,4,6-trimethylpyridine (collidine)
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethylazodicarboxylate
DHP	3,4-dihydro-*2H*-pyran
DIAD	diisopropylazodicarboxylate
DIBAL	diisobutylaluminumhydride
DIPT	diisopropyl tartrate
4-DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DMTST	(dimethylthio)methylsulfonium trifluoromethane sulfonate
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
DTBMS	di-*tert*-butylmethylsilyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EVE-Li	2-lithio-ethylvinylether
FMOC	9-fluorenylmethoxycarbonyl
FMPTS	2-fluoro-1-methyl pyridinium tosylate
HMDS	bis(trimethylsilyl)amide
HOAt	7-aza-1-hydroxy-1*H*-benzotriazole
HOBt	1-hydroxybenzotriazole
IBX	*o*-iodoxybenzoic acid
IDCP	iodobis(collidine) perchlorate
im	imidazolyl
imid	imidazole
KSAE	Katsuki–Sharpless asymmetric epoxidation
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
lut	2,6-dimethylpyridine (lutidine)
*m*CPBA	3-chloroperoxybenzoic acid
MOM	methoxymethyl
MOP	3-methoxypyridyloxy
MP	4-methoxyphenyl
Ms	methanesulfonyl
NB	nitrobenzyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine-*N*-oxide
PBS	phosphate-buffered saline
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protecting group
Phth	phthaloyl
Piv	pivaloyl
PMA	phorbol 12-myristate 13-acetate
PMB	*p*-methoxybenzyl
PPTS	pyridinium 4-toluenesulfonate
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
SAE	Sharpless asymmetric epoxidation
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammoniumperruthenate
TPS	triphenylsilyl
Tr	triphenylmethyl (trityl)
Ts	4-toluenesulfonyl (tosyl)
UDP	uridine-5′-diphosphate

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