

Tetrahedron: *Asymmetry* report number 89

Synthesis of a 28-mer oligosaccharide core of *Mycobacterium lipoarabinomannan* (LAM) requires only two *n*-pentenyl orthoester progenitors

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Dedicated to Professors Clinton E. Ballou and Y. C. Lee for their pioneering work on the elucidation of the structure of mycobacterial LAMs

Abstract—Regioselective glycosidation of acceptor polyols greatly reduces the number of orthogonal protecting groups that are normally required for conventional syntheses of highly branched oligosaccharides. The MATCH between a donor and one of the many-OHs is the basis of a simple, ready synthesis of the 28-mer oligosaccharide described in this manuscript. The strategy relies heavily upon the unique interplay between *n*-pentenyl orthoesters (NPOEs), *n*-pentenyl glycosides, ytterbium triflate, and *N*-iodosuccinimide which allows exquisite, high-yielding regio- and chemoselective glycosylations. The NPOEs, effective as mannose or arabinose donors, are the sole sources of all saccharide components of the lipoarabinomannan oligosaccharide. Once *considerable systematic research* had been invested, the 12-mer mannan, **92**, and 16-mer capped arabinan, **91**, domains can be rapidly assembled in 300 mg and 1 g quantities, respectively, using conventional laboratory equipment. The 28-mer, **93** (MW = 11122.54) is, as far as we are aware of, the largest hetero-oligosaccharide that has been synthesized.

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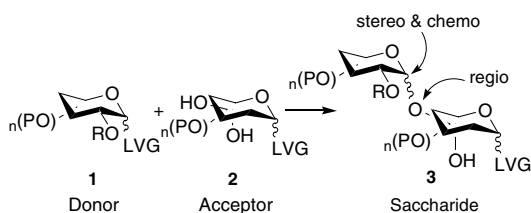
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1. Introduction

Oligosaccharide synthesis is no longer the fringe activity that it was in 1982, when Paulsen reviewed the field.¹ In the 18 pages of that article, the main donors discussed, were glycosyl bromides and chlorides, **1** (LVG = Br and Cl). Although thioglycosides had been introduced by Ferrier years earlier,² ‘sulfur-containing leaving groups’ were covered in ten lines. Glycosyl imidates, **1** (LVG = O(Me)=NMe), had just been introduced by Sinaÿ et al.,³ and Schmidt’s seminal improvements had not yet taken hold.⁴ Of the three selectivities depicted in the fundamental process of oligosaccharide synthesis summarized in Scheme 1, stereoselectivity was the only one that received concentrated study, the options available being neighboring group participation, use of soluble or insoluble silver salts, and halide ion catalysis.

Given this small data base relating to Scheme 1, it may have seemed judicious for Paulsen to have warned that ‘it should be emphasized that each oligosaccharide synthesis remains an independent problem, whose resolution requires considerable systematic research and a good deal of know how. There are no universal reaction conditions for oligosaccharide synthesis’.



Scheme 1. Selectivities in glycosyl couplings.

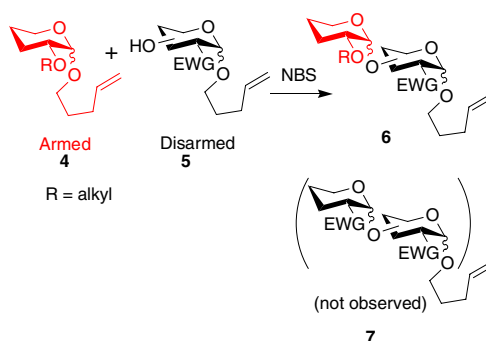
However, in spite of the burgeoning number of options⁵ for LVG in **1**, that caveat remains valid two decades later. Thus a behind-the-scenes look at the spectacular achievements of oligosaccharide syntheses, whether solution,⁶ solid phase,⁷ automated,⁸ or programmed,⁹ will reveal that ‘considerable systematic research’ had gone into the activity. The same holds even for Nishimura’s elegant chemo-enzymatic automated procedures.¹⁰

The apparent simplicity of coupling **1** with **2** disguises the fact that the process involves three of the four selectivities, namely chemo, stereo, and regio, that, according to Trost,¹¹ confront general organic synthesis. The fourth, enantioselectivity, is usually irrelevant since for most targets, the configurations of **1** and **2** are dictated by nature.

The bond being formed in **3** is subject to chemo- and stereocontrols. Since Isbell’s seminal paper in 1940,¹² the major stereocontrolling implement has been the protecting group at O2 of the donor. That trend continues as apparent from the recent examples (a) from Boons’ laboratory, where anomeric stereoselectivity is controlled by the chirality of an O2 ether substituent¹³ and (b) Demchenko’s use of 2-*O*-picolyl STaz donors to control for β selectivity.¹⁴

1.1. Protecting groups do more than protect

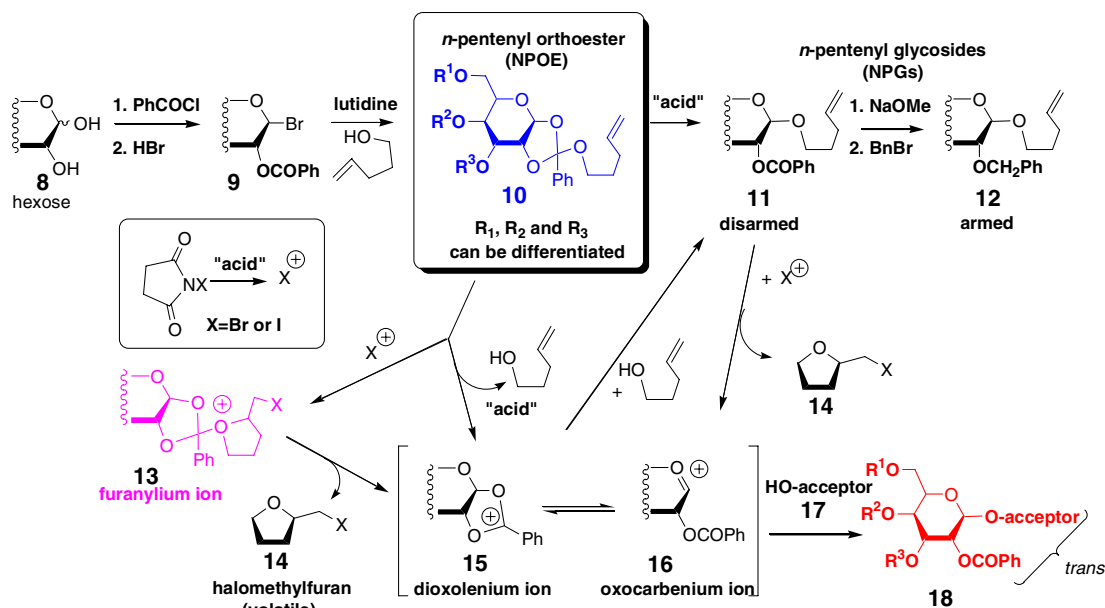
Isbell’s insight anticipated present awareness that protecting groups affect all three selectivities of the reaction in Scheme 1. That protecting groups do more than protect was impressed upon us in 1988, with the story summarized in Scheme 2. Individually, the *n*-pentenyl glycosides (NPGs) **4** and **5** served as perfectly good donors toward an acceptor.¹⁵ However, when forced into competition, as in Scheme 2, the erstwhile donor **5** was forced to become an acceptor to **4** with the result that the cross-coupled product **6**, was formed, sometimes to the exclusion of the self-coupled alternative **7**.¹⁶ Donors **4** and **5** were said to be ‘armed’ and ‘disarmed’, respectively, in view of their roles in Scheme 2.



Scheme 2. Armed and disarmed concept in glycosyl couplings as initially described with *n*-pentenyl glycosides.

Notably, in the original meaning, the ‘disarmed’ unit of product **6** could be changed to an ‘armed’ entity so as to readily serve as a glycosyl donor.¹⁶

The deactivating effect of esters versus ether protecting groups upon sugars had been noted in Paulsen’s article.¹ But the first demonstration that these differences could be exploited for synthetic advantage was made with *n*-pentenyl glycosides.¹⁶ The armed/disarmed principle has been extended to many other donors,¹⁷ and continues to inspire mechanistic investigation.¹⁸ The concept is now presented



Scheme 3. The *n*-pentenyl family of glycosyl donors.

in text books,¹⁹ and has become so embedded in the fabric of carbohydrate chemistry that, 20 years later, citations are usually omitted.

The above demonstration of chemoselectivity in oligosaccharide synthesis (Scheme 2), was quickly followed by another which is based on the ‘disarming’ effect of widely used cyclic acetal protecting groups.²⁰ The latter effect, which is described as ‘torsional armed/disarmed strategy’ to distinguish it from the electronic modality (Scheme 2), has proved pivotal in the scholarly route to β -mannosides developed by Crich.²¹

1.2. The *n*-pentenyl family of glycosyl donors

In view of the foregoing, it is appropriate to describe some features of the *n*-pentenyl family of glycosyl donors.

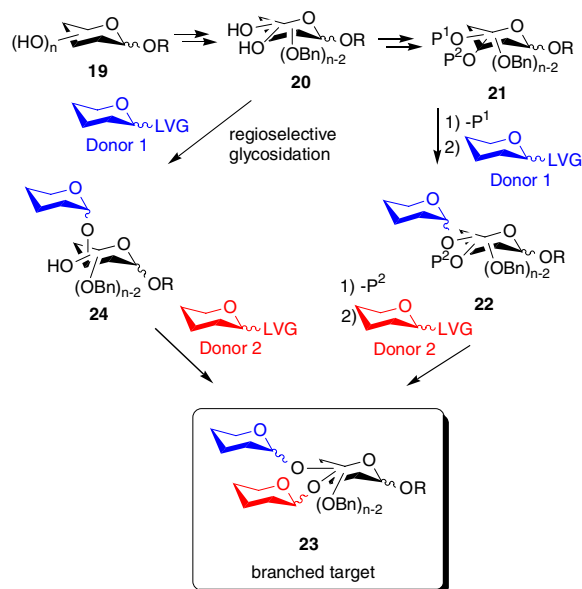
Glycosyl orthoesters such as **10** can be readily prepared from an aldohexose in three steps, as indicated in Scheme 3. Interestingly, the first compound of this type was isolated by Fischer et al. in 1920,²² although it took a decade²³ for its structure to be elucidated. Since then, glycosyl orthoesters have been used extensively to prepare *trans*-1,2-glycosides by acid catalyzed rearrangement (e.g., **10** \rightarrow **11**). The disarmed donor, **11**, so obtained can then be readily converted into the armed counterpart, **12**.

The advent of *n*-pentenyl chemistry²⁴ added a dimension to the capability of glycosyl orthoesters, that Kotchetkov, the major exponent of glycosyl orthoester chemistry, had found wanting.²⁵ Thus the *n*-pentenyloxy moiety (a) could not only be transferred to the anomeric center by the normal rearrangement, **10** \rightarrow **11**, but (b) could be extricated via the furanylium ion, **13**, into the halomethyl furan **14**, so that an in situ acceptor, **17**, would not face competition in providing a new glycoside **18**.

Of course the latter, **18**, could alternatively have been obtained from the disarmed donor **11** via the oxocarbenium ion **16**, but the low reactivity sometimes causes iodo-alkoxylation of the double bond of disarmed **11**. Such products are never obtained with NPOEs.

2. Regioselectivity

However, protecting groups are a necessary evil, and the menace they pose can be seen for the branched target **23** (Scheme 4). For a polyol such as **19**, the standard



Scheme 4. Regioselective glycosylation versus protecting group based strategy in oligosaccharide synthesis.

procedure would be to install ‘permanent’ protecting groups (usually benzyls) in **20** on the hydroxyl groups which are of no interest, and ‘temporary’ orthogonal groups, P¹ and P², in **21**. This preemptive protocol is designed to ensure that only one-OH is exposed and presented to each donor at the required time.

However, the selective installation and removal of P¹ and P² not only adds steps, but enhances anxiety, because as the size of a synthetic oligosaccharide grows, P¹ and P² can become immersed in a sea of ‘permanent’ protecting groups, which can induce uncharacteristic responses.

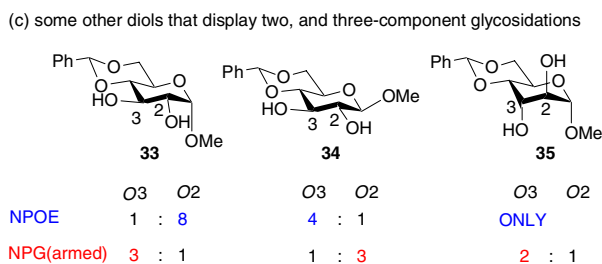
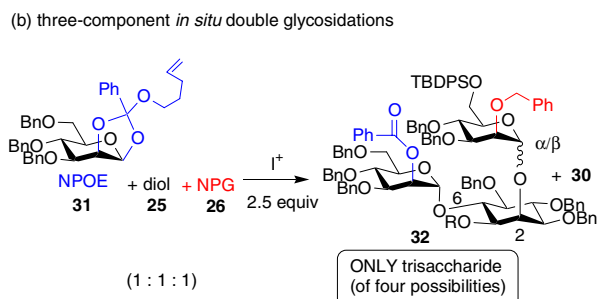
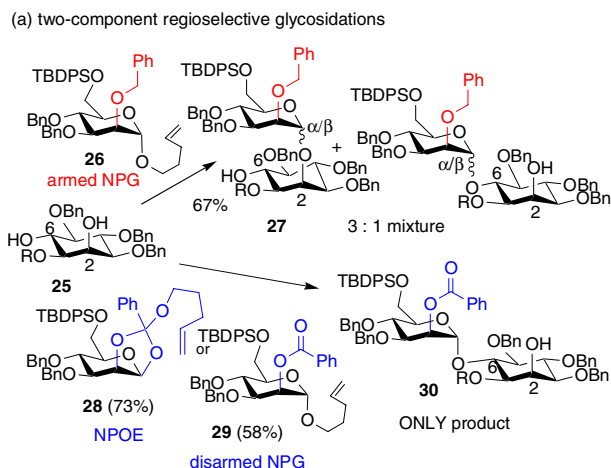
Regioselective glycosidation would obviate the need for orthogonal protecting groups, leading stepwise from **20** → **24** → **23**.

Our interests in this possibility emanated from the recent observations in our laboratory summarized in Scheme 5a.²⁶ In the hope of achieving selective glycosidation of

the equatorial-OH, we treated diol **25** with the armed *n*-pentenyl donor **26**. However, the major product was the mixture of α/β glycosides **27** from glycosidation at the axial-OH. We surmised that the corresponding disarmed donor, **29**, would improve α anomeric stereoselectivity because of neighboring group participation; but most surprisingly, the only product was now the disaccharide **30** from glycosidation at the equatorial-OH.

From Scheme 3, it is seen that NPOE **10** and NPG **11** lead to the same manifold of intermediates, **15** and **16**. Accordingly, we found that NPOE **28** also gave disaccharide **30** exclusively indeed with the improved yield of 73%.

The observed regioselectivity could not be justified by evoking any permutation of the usual steric and/or reactivity considerations. Thus with regard to donor reactivity, our laboratory has developed procedures for quantitatively determining the relative reactivity of *n*-pentenyl donors.²⁷ The ranking is: **28** \ggggg **26** > **29**. Thus, the most and least reactive donors display the same regioselectivity for the equatorial-OH of **25**.



2.1. The concept of MATCH

The anomalies in Scheme 5a caused us to revisit the concept of MATCH between a donor and an acceptor that had been expressed by Paulsen 30 years ago,²⁸ to reflect the wisdom gained in the minefield of early oligosaccharide synthesis. Extensive experience had taught Paulsen that poor yield from a given donor/acceptor pair could be improved by switching donors. An ‘explanation’ for such MATCH was not offered—but its validity emerged from trial and error experiments in keeping with the best traditions of classical, experimental synthetic organic chemistry.

However, the concept of MATCH as introduced by Paulsen,²⁸ referred to the *yield* in the reaction of one donor/acceptor combination versus another. The issue of regioselectivity was not considered. Indeed the issue was not raised systematically for another 20 years.²⁹

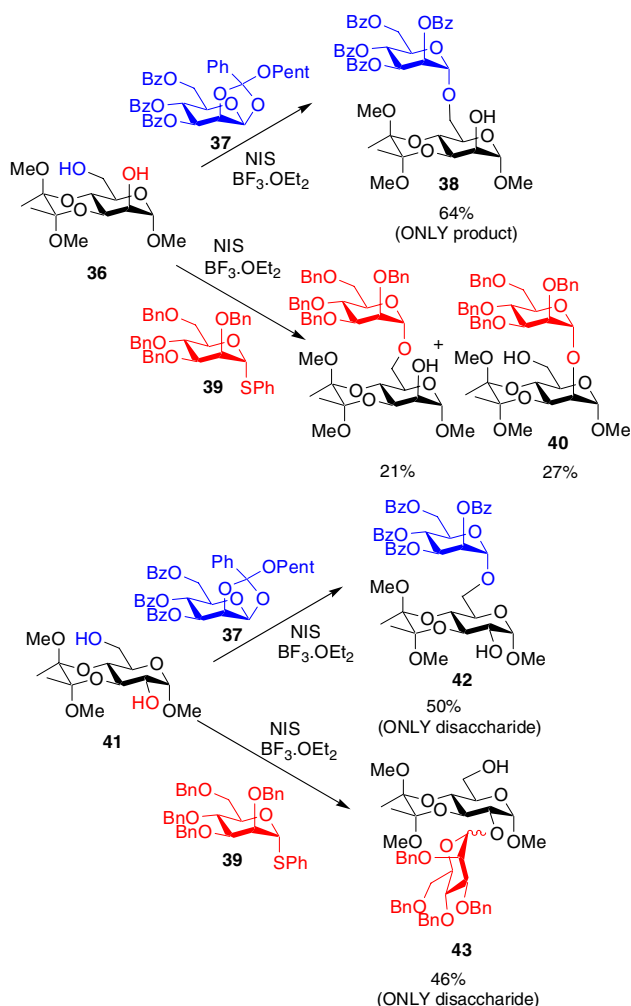
In an exquisite demonstration of MATCH induced regioselectivity, diol **25** was presented to both donors NPOE **31** and NPG **26**, in an *in situ*, three component competitive milieu²⁶ (Scheme 5b). Only one pseudotrisaccharide, **32**, of the four possibilities was obtained, in which each donor had gone to its preferred-OH as seen in Scheme 5a.

Several other diols have been tested and found to exhibit MATCH for NPOEs versus armed NPGs. The tabulated two-component results for the diastereomers **33**–**35** shown in Scheme 5c, are typical. In two-component reactions, one of the –OH groups, is favored by the NPOE, and the other by armed NPG. Three-component, *in situ* double glycosidations have also been observed for these diols, and in the case of **35**, impressive optimizations of the lone trisaccharide formed, provide powerful support for the concept of MATCH.³⁰

Scheme 5. Regioselective glycosyl couplings based on the nature of the O2 substituent in the glycosyl donor. Application to three component *in situ* double glycosylations.

2.2. Primary versus secondary hydroxyls

As noted above, the regioselectivities in Scheme 5a could not be rationalized on the basis of the usual criteria such as steric hindrance. We decided to test regioselective MATCH with the pair of butane diacetal³¹ primary/secondary diols, **36** and **41**.³² The results in Scheme 6 show that the NPOE, **37**, is exquisitely selective for the primary-OHs in both cases, giving **38** and **42**, while the armed thioglycoside, **39**, favors the secondary-OH, giving **40** in slight excess in the case of **36**, and exclusively **43** in the case of **41**.³² (It should be noted that thioglycosides and NPGs exhibit the same regio-preferences.³³)



Scheme 6. Primary versus secondary hydroxyl regioselectivities.

3. A revolutionary role for lanthanide triflates

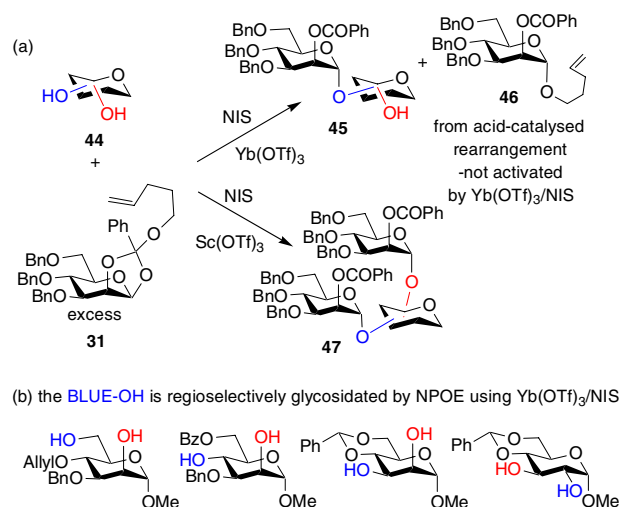
Scheme 3 shows that an ‘acid’ is used (a) for NPOE rearrangement $\mathbf{10} \rightarrow \mathbf{11}$ and (b) to generate iodonium ion (I^+) needed for *n*-pentenyl activation. Problems were sometimes encountered with acid sensitive protecting groups on the substrates, and we hoped that these could be avoided by the use of lanthanide salts. Indeed we found that several

lanthanide triflates could serve, independently, for (a) the rearrangement and (b) generation of I^+ .³⁴

These data must be viewed in the context of Scheme 3. In the presence of the ‘acid’ and I^+ , the NPOE, **10**, is partitioned between NPG **11** (through loss followed by recapture of the pentenyl-OH), and the furanylium ion **13**, the latter being destined to glycosidate the acceptor-OH.

However, an unexpected benefit came from chemoselective glycosidations allowed by these salts. Thus, $\text{Yb}(\text{OTf})_3/\text{NIS}$ was found to induce glycosidation with NPOEs but NOT NPGs, whereas $\text{Sc}(\text{OTf})_3/\text{NIS}$ induced glycosidation with both NPOEs and NPGs.³⁵

The highly utilitarian value of this discrimination is demonstrated in Scheme 7a.³⁵ Diol **44** can be treated with excess NPOE **31** in the presence of $\text{Yb}(\text{OTf})_3/\text{NIS}$ so as to optimize regioselective monoglycosidation leading to **45** (Scheme 7a). Any disarmed NPG **46** produced, being refractory to the reaction medium, would not threaten the free-OH of **45**.



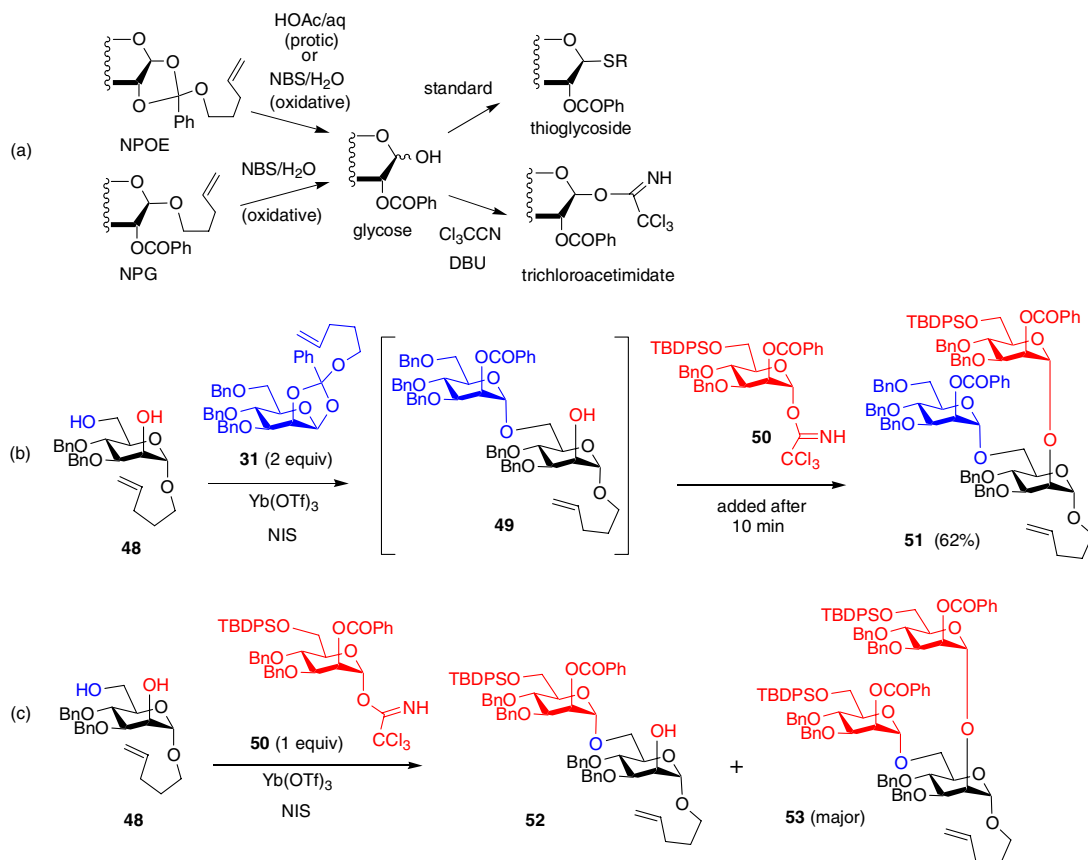
Scheme 7. Lanthanide triflates in glycosyl couplings.

However, since $\text{Sc}(\text{OTf})_3/\text{NIS}$ also activates disarmed NPGs, the reaction in Scheme 7b would lead to substantial amounts of the double glycosidation product **47**.

These lanthanide based chemoselectivities were tested on several other diols, and the samples collected in Scheme 7b show that the discrimination holds for primary versus secondary, as well as secondary versus secondary diols.

3.1. Orthogonal $\text{Yb}(\text{OTf})_3$ -based chemo- and regioselective glycosylation

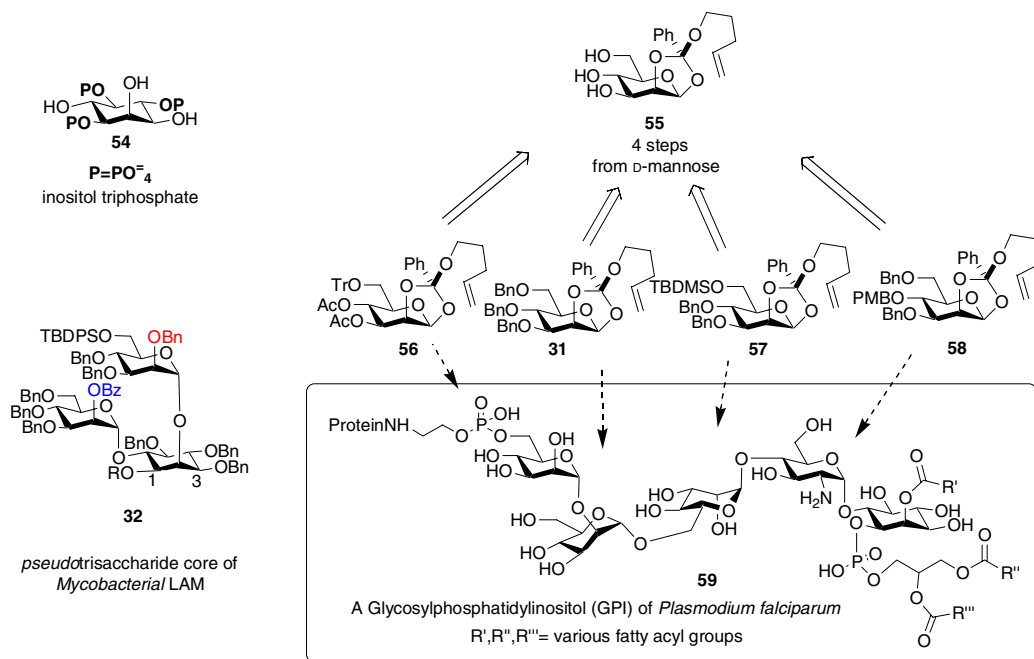
Further advantage of lanthanide salts arose from the discovery that although $\text{Yb}(\text{OTf})_3/\text{NIS}$ does not activate NPGs, it does activate ethyl thioglycosides and trichloroacetimidates. Both of the latter donors can be readily obtained from NPOEs or NPGs by protic or oxidative



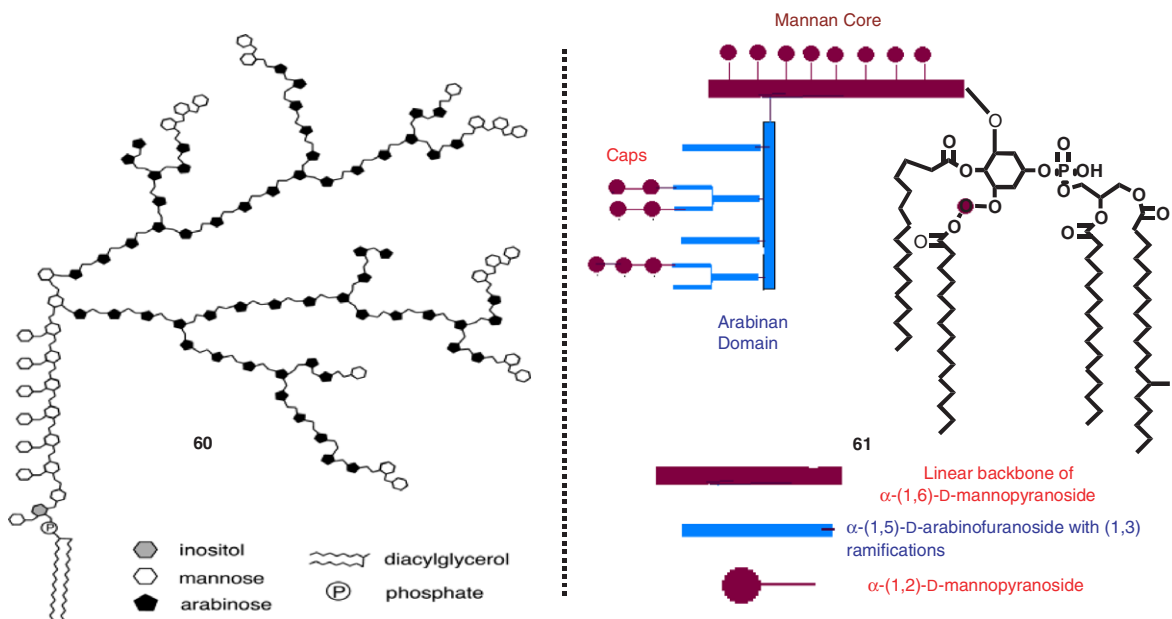
Scheme 8. One-pot glycosylation based on $\text{Yb}(\text{OTf})_3$ chemoselective couplings.

hydrolysis as shown in [Scheme 8a](#). This behavior toward $\text{Yb}(\text{OTf})_3$ permits the sequential procedure depicted in [Scheme 8b](#), that blends all three selectivities. Thus the

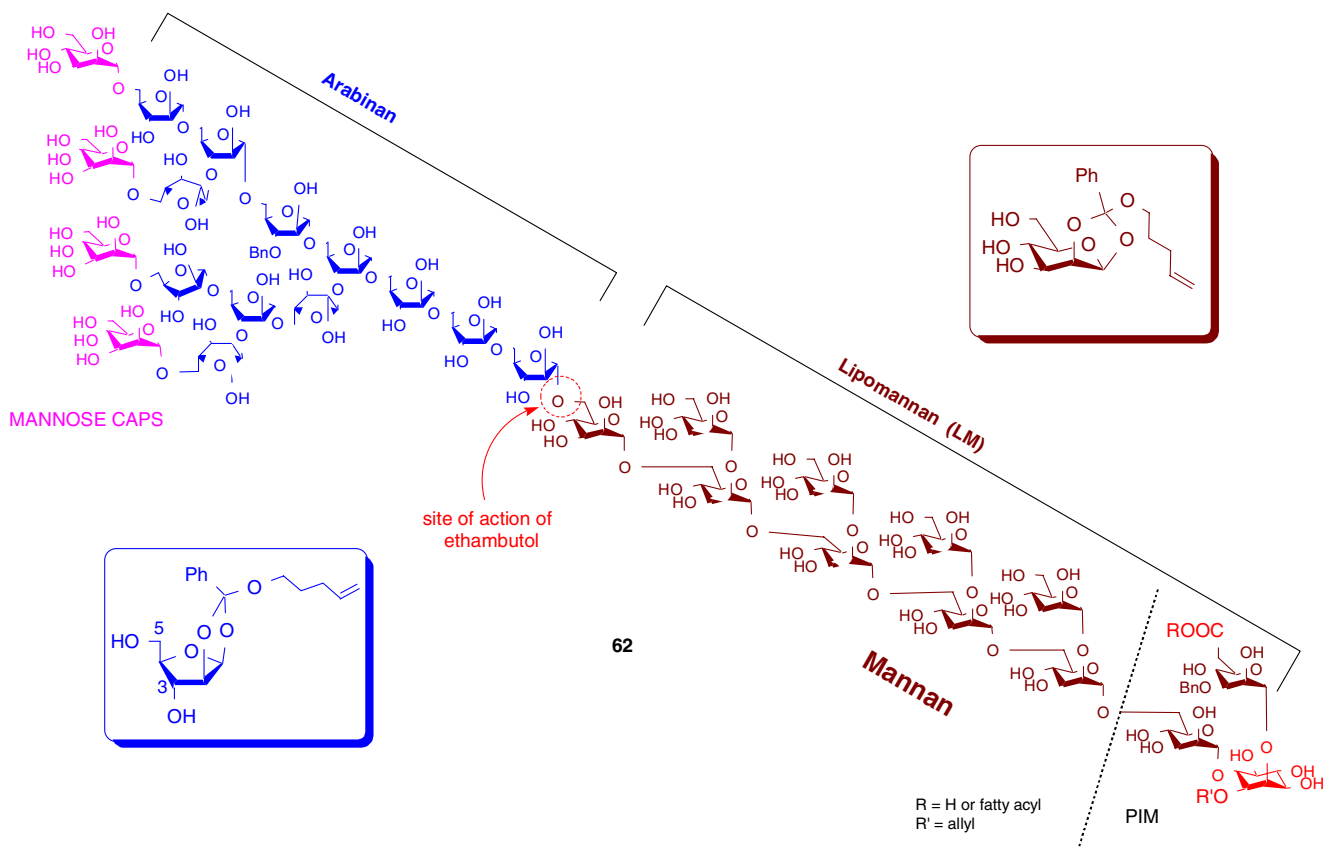
NPG acceptor diol **48** reacts chemo- and regioselectively with NPOE **31** to permit optimization of **49**, and after 10 min, the trichloroacetimidate **50**, prepared from the



Scheme 9. First synthesis of a malaria GPI, **59**.



Scheme 10. Cartoons of *Mycobacterial lipoarabinomannans* (LAMs).



Scheme 11. Mannose 'Capped' 28-member arabinomannan.

corresponding NPOE as illustrated in Scheme 8b, was added. The α,α linked trisaccharide **51** was obtained in 62% yield.³⁵

In passing we note (a) that phenyl thioglycosides were not activated by $\text{Yb}(\text{OTf})_3/\text{NIS}$, this discrimination being in

keeping with early observations of Garegg et al.,³⁶ and (b) that Adinolfi et al.³⁷ have reported on the use of lanthanide triflates to activate trifluoroacetimidate donors.

The importance for donor based selectivity is seen in the contrast between Scheme 8b and 8c. The use of excess

NPOE **31** with $\text{Yb}(\text{OTf})_3/\text{NIS}$ gave **49** only. However, with only 1 equiv of the trichloroacetimidate **50**, a mixture of single and double glycosidation products, **52** and **53** was given, the latter being the major.

4. Inositol biomolecules

Our interest in inositol biomolecules began with a synthesis of inositol triphosphate, **54**, in 1988.³⁸ In that same year, *n*-pentenyl glycosides (NPGs) were discovered,³⁹ and Ferguson's elegant structure elucidation of a glycosyl phosphatidyl inositol (GPI) was reported.⁴⁰ In light of the latter coincidence, GPI phosphoinositides became the foci for developing NPG methodology,⁴¹ and that association was rewarded with (one of) the first total syntheses of a GPI.⁴²

A tangent led us to the inositol dimannoside **32** (Scheme 5) from which our above-described concern with regioselective glycosidation and MATCH emanated. This concept was the basis of the first syntheses of a malarial GPI, **59**,⁴³ and prototypes thereof.⁴⁴ The retrosynthesis in Scheme 9 emphasizes the versatility of *n*-pentenyl orthoesters (NPOEs), upon which we drew further in the studies below.

5. Tuberculosis

Tuberculosis, which has been one of the world's most ruthless killers for millennia,⁴⁵ is currently seeing a resurgence in a multiple drug resistant (MDR)⁴⁶ and extremely drug resistant (XDR)⁴⁷ manifestations that are rendered more devastating because of their synergy with AIDS.⁴⁸ The threats to underprivileged, underserved 'third world' populations is well chronicled,⁴⁹ and fits with the founding ethos of the Natural Products and Glycotechnology (eponymously NPG) Research Institute as a non-profit agency for investigating the oligosaccharides of 'third-world' diseases.

5.1. Multiple facets of lipoarabinomannans

Brennan has described the cell surface coat of *Mycobacterium tuberculosis* as a 'treasure house of unusual compounds'⁵⁰ and our scientific interest was tweaked by cartoons **60** and **61** by Chatterjee⁵¹ and Puzo⁵² (Scheme 10) that convey the horrendously complex lipoarabinomannan (LAM) surface glycolipid. This glycolipid occupies a central place in heroic efforts to combat tuberculosis, for it protects the pathogen against detection,⁴⁵ thereby inhibiting diagnosis in bygone days, until the belated sign of blood streaked sputum revealed the advanced stage of the disease. Koch's breach of LAM in 1882 was a monumental achievement,⁵³ but structure elucidation, even now still tentative, has had to await recent state-of-the-art technological developments.^{54,55}

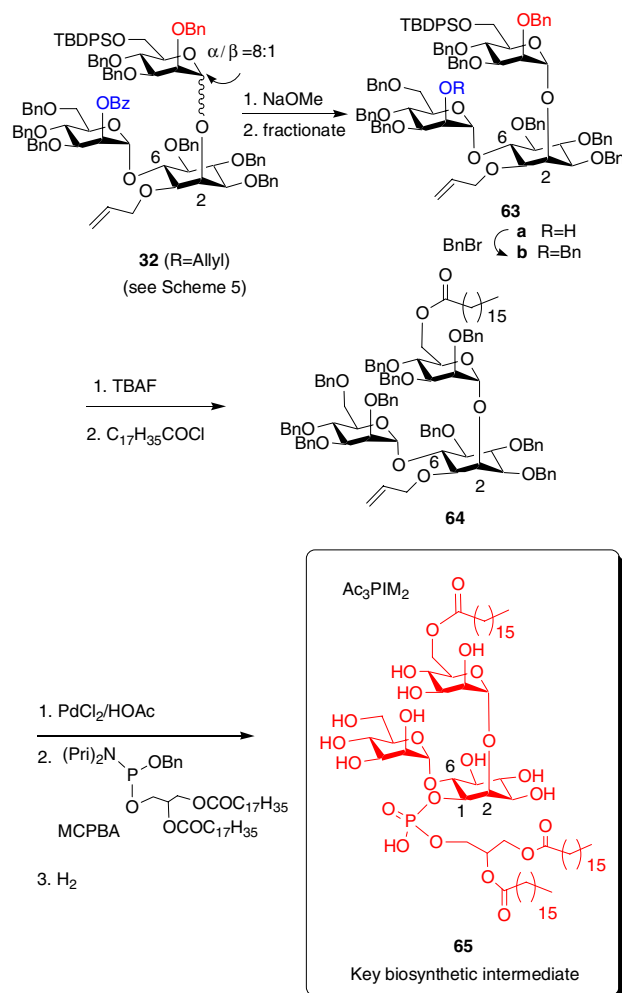
However, *M. tuberculosis* is only one species of a genus that includes other infamous pathogens, for example, *Mycobacterium leprae*, *Mycobacterium vaccae*, *Mycobacterium bovi*,

and *Mycobacterium avium* and, on the other hand, clinically used *Mycobacterium smegmatis*,⁵⁶ all of which appear to have the same gross LAM structure. Indeed, cartoons **60** and **61** represent composites derived from structural studies of various mycobacterial LAM isolates. Most significantly, biological differentiation between various LAMs seems to be imparted by 'caps' at the distal extremities (e.g., the mannoses in **60** and **61**).

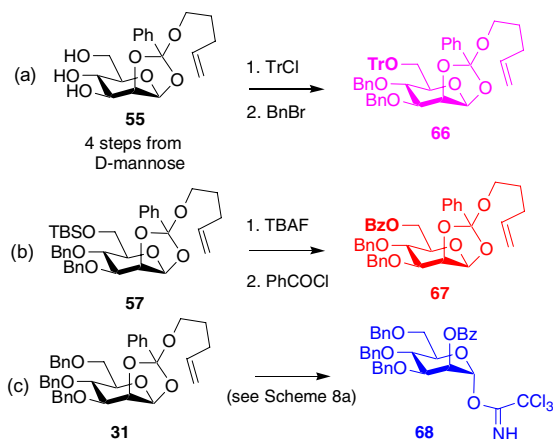
In addition to tuberculosis and leprosy, LAM has been associated with a range of health disorders including, allergic asthma,⁵⁷ herpes,⁵⁸ cancer,⁵⁹ bladder cancer,⁶⁰ and has even been found to potentiate anti-HIV retrovirals.⁶¹ Thus the multifaceted structure, depicted in cartoons **60** and **61**, is matched by multifarious biological activity.

Could the interrelationship of structure and activity of these LAM be deconstructed.

The challenge to synthetic organic chemistry is to provide samples of unquestionable provenance,⁶² and to appreciate better the task at hand, cartoons **60** and **61** were rendered as the 28-mer oligosaccharide **62**. The prospects for this task may be judged from the very recent comments of



Scheme 12. Key biosynthetic intermediate **65**.



Scheme 13. NPOE building blocks for the synthesis of **73**.

Nigou, a member of the eminent mycobacterial CNRS laboratory in Toulouse, that ‘synthesis of the lipomannan portion (see Scheme 10) can hardly be envisaged’.⁵⁵

As indicated in Scheme 11, the major disconnection of the LAM structure **62** coincides with the site where the popular antituberculosis drug, ethambutol, is thought to operate. This convenient disconnection gives the lipomannan (LM) on the ‘right-hand side’ which in turn can be further

disconnected into mannan and phosphatidyl inositol mannoside (PIM) domains.

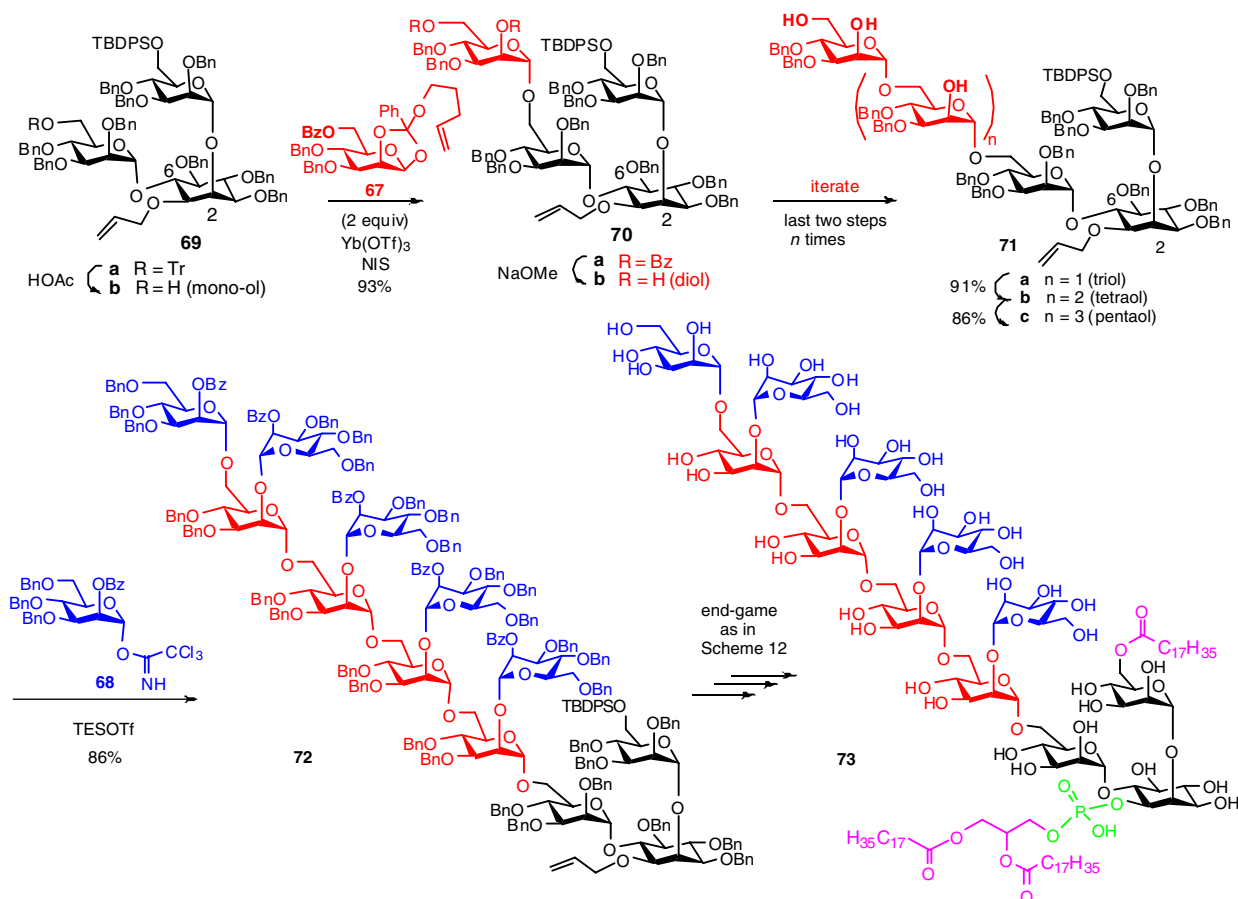
This was a good place to begin, since PIM constitutes a major intermediate in the biosynthesis of LAM.⁶³

6. First synthesis of Ac_3PIM_2

The synthetic approach to PIM benefited from the regioselective glycosidation studies in Scheme 5a and b. Debenzoylation of the 8:1 α/β mixture, pseudotrisaccharide **32**, allowed separation of the pure diastereomer, **63a**, and standard processing of the protecting groups freed the primary hydroxyl group for fatty acylation leading to **64**. Deallylation followed by phospholipidation, using our time-tested protocol,³⁸ afforded the triacylated phosphorylated inositol dimannoside, Ac_3PIM_2 , **65**.⁶⁴

7. First synthesis of a lipomannan (LM)

The ready, succinct route to **65** encouraged us to tackle the mannan domain of **62**. First, an analog of **63** was required, in which the primary-OHs of both mannosides were differentiated, the ‘right-hand-one’ (i.e., on O2) needed for eventual fatty acylation, and the ‘left-hand-one’



Scheme 14. First synthesis of a lipomannan (LM).

for developing the mannan array. On the basis of trial and error, NPG **26** (see Scheme 5a) was retained for O2 mannosylation, while a 6-O-tritylated NPOE, **66** (Scheme 13a), proved to be the best candidate for the O6 mannoside. Sequential glycosidations, followed by processing, as in Scheme 12, afforded pseudotrisaccharide **69a**, and detritylation gave the mono-ol **69b**, ready for elaboration of the mannan domain.

As noted above in connection with Scheme 4, a multi-branched array, such as that seen in compound **62**, normally requires a shuttle of orthogonal protecting groups in order to ensure that a single-OH is presented to each donor at any time. However, the systematic research related to MATCH, especially the exquisite regioselective advantage proffered by Yb(OTf)₃/NIS summarized in Scheme 7, suggested a way to avoid many of the protection/deprotection episodes. In this connection, the preliminary studies for the 2,6-mannosidyl diol **48** (Scheme 8b) were paramount, since an excess of an NPOE could be used to optimize regioselective glycosidation at the primary-OH, without threatening the secondary-OH.

Accordingly, the NPOE **67** (Scheme 13b) was the donor of choice since it had two benzoate groups—one formal and one latent. Glycosidation of **69b** therefore afforded the dibenzoate **70a**, in near quantitative yield, and thence diol **70b**. Iterative regioselective mannosylation with NPOE **67**, followed by saponification led from diol **70b** to triol **71a**, to tetraol **71b**, and thence pentaol **71c**, the excellent yields being maintained throughout.

All five-OHs of **71c** now had to be mannosylated. Trial and error showed that a trichloroacetimidate would be the best donor for this purpose, and so donor **68** (prepared from NPOE **31** as outlined in Scheme 8a), afforded dodecasaccharide **72** in 86% yield.

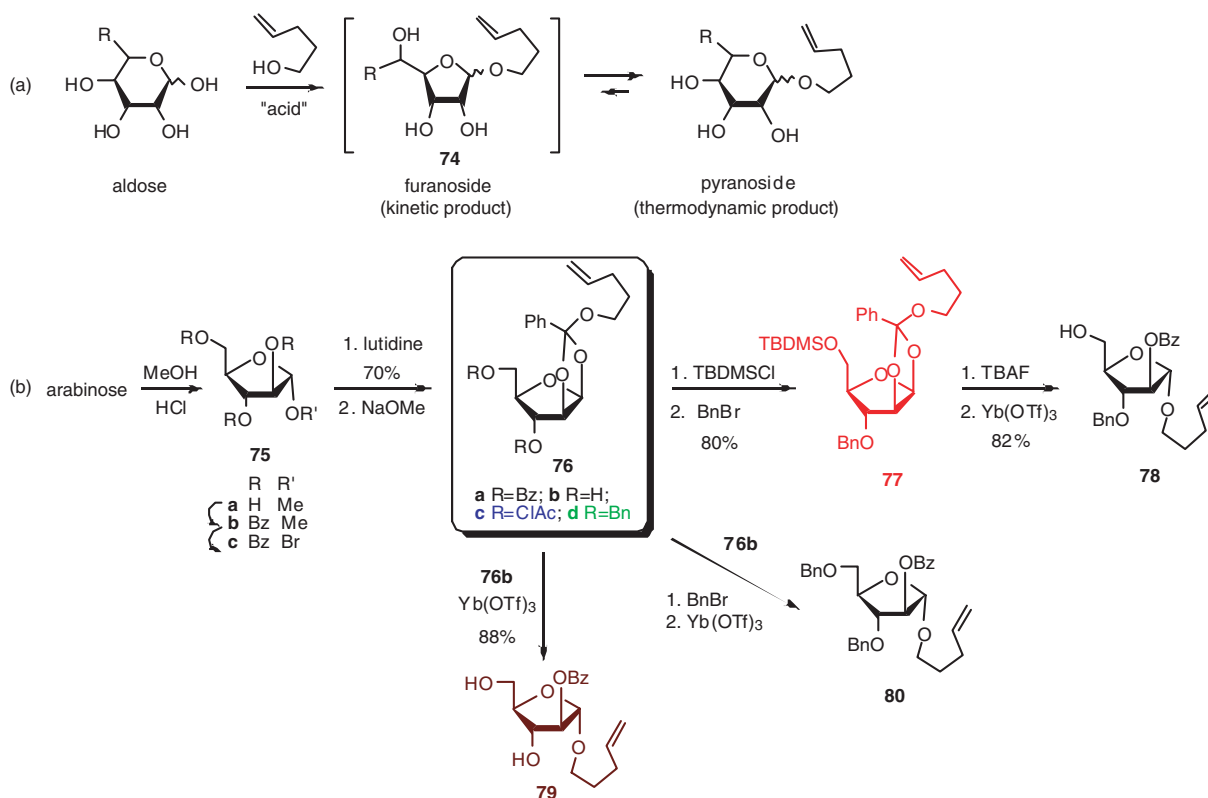
The protecting group manipulations that had been tested for the end game to **65** (Scheme 12), were again successfully applied to obtain the lipomannan **73**.⁶⁵

The efficiency of the synthetic route in Scheme 14 may be judged by the fact that one postdoctoral fellow can prepare 300 mg of the dodecasaccharide **72** in 3 weeks, once the ‘considerable systematic research’, of which Paulsen cautioned, had been carried out.

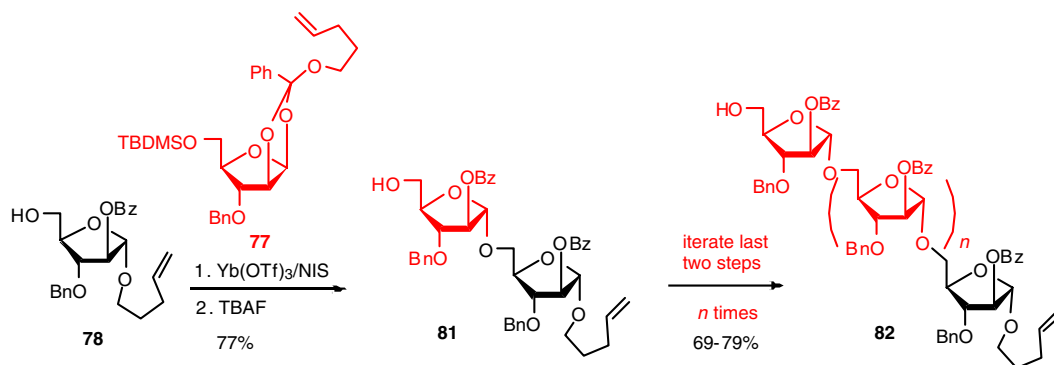
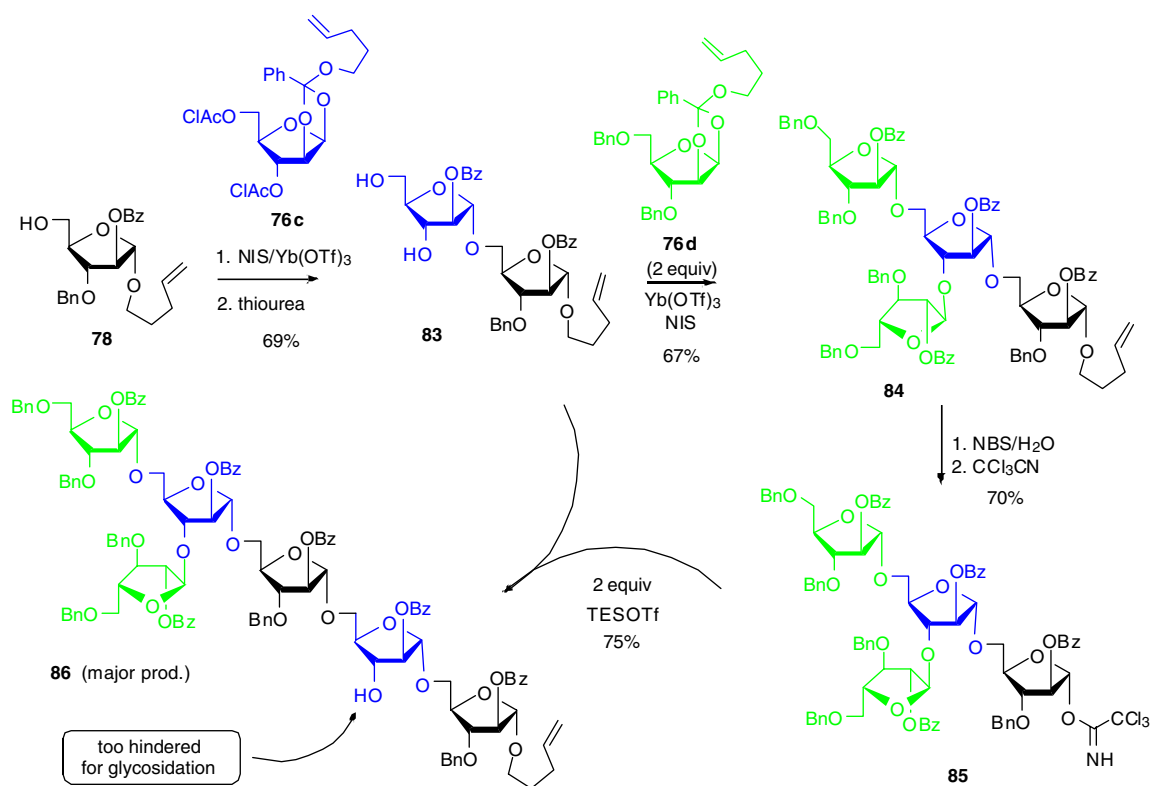
8. The arabinan domain

The arabinan domain of **62** (Scheme 11) possesses furanose units, linked α -1,5-linearly, with occasional O3 branches. Furanose chemistry was uncharted territory to us. Unlike pyranosides, furanoses have attracted comparatively little attention because they have been isolated less frequently from nature. However this circumstance may be due to the fact that furanoses are much less robust, and thus may not have survived traditional methods of isolation.

Furanosides are kinetic products in Fischer glycosidations, and in the case of simple alcohols, such as methanol, good



Scheme 15. *n*-Pentenyl furanose donors.

Scheme 16. Synthesis of linear arabinan **82**.

Scheme 17. First attempt at branched arabinans.

yields can be obtained by quenching the reaction at the opportune stage. We adopted this approach in 1995 for preparation of *n*-pentenyl furanosides (Scheme 15a), but yields of structures such as **74** were never satisfactory.⁶⁶

Given the successful use of pyranose orthoesters above for the mannan domain (Scheme 14), we were encouraged to extend this methodology to the preparation of furanosides. However, the synthetic procedure depicted in Scheme 3 favors pyranose rings and so would not be applicable for obtaining furanose orthoesters.

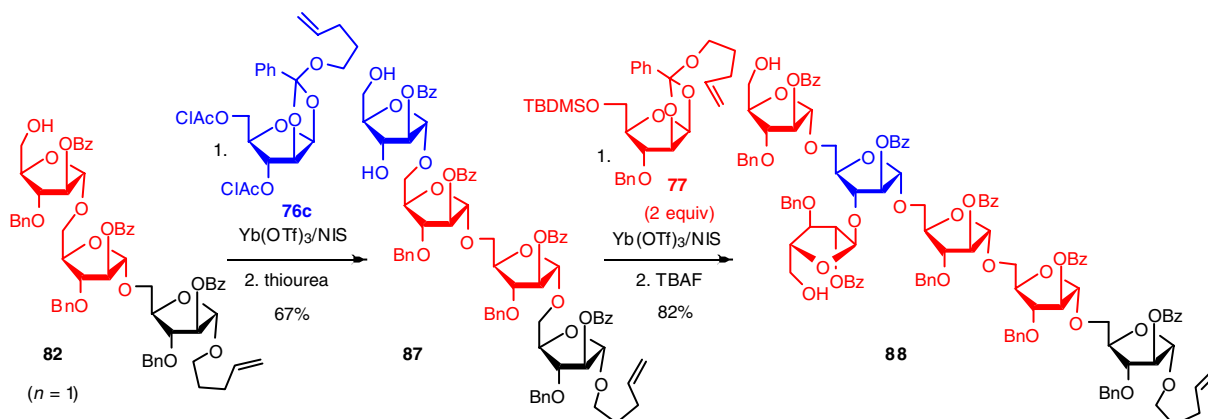
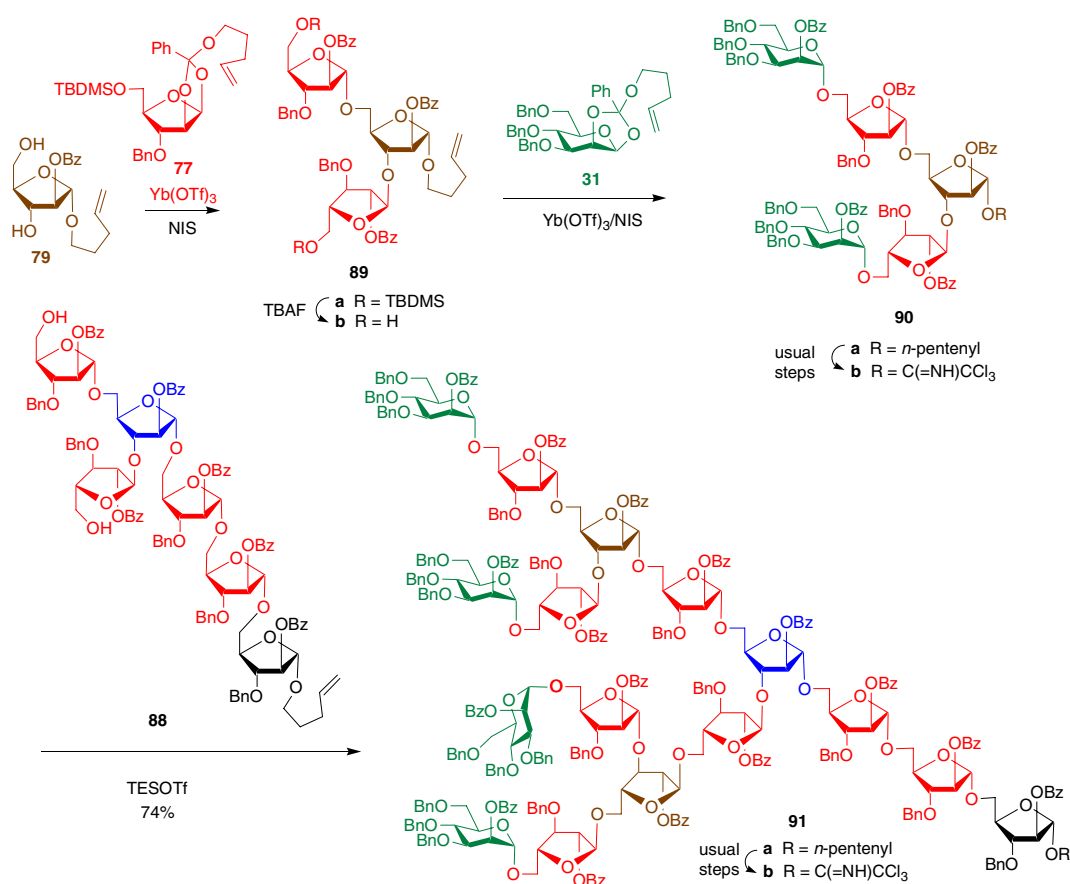
The alternative approach began with methyl arabinofuranoside, **75a**, which can be readily obtained by Fischer glycosidation.⁶⁷ (The material is also commercially available.) In view of the compound's acid lability, perbenzoyl-

ation to **75b**, was employed to prevent ring expansion during treatment with HBr to obtain the furanosyl bromide **75c**. Treatment of the latter with lutidine then afforded orthoester **76a**, and thence the corresponding diol **76b**.

From this diol, the various donor and acceptor precursors, for the linear and branched units, could be readily crafted by the judicious combination of protecting group manipulations coupled with the (now) classical NPOE → NPG rearrangement, leading to **78–80** (Scheme 15b).

8.1. Linear motifs

The simple procedure for obtaining a linear array, as summarized in Scheme 16, involves, step 1, coupling of **78** with

Scheme 18. Synthesis of branched arabinan **88**.

Scheme 19. Assembly of the mannose capped arabinan domain.

77, followed (step 2), by desilylation to obtain **81**. Iteration of steps 1 and 2 then gives compound **82**, *n* being any number desired.⁶⁸

8.2. Branched motifs

A strategy for the branched motif was tested using the chloroacetylated NPOE **76c** (Scheme 17) which readily reacted with **78** to provide two free-OHs in **83**. The latter

reacted smoothly with 2 equiv of NPOE **76d** to give the tetrasaccharide **84**.

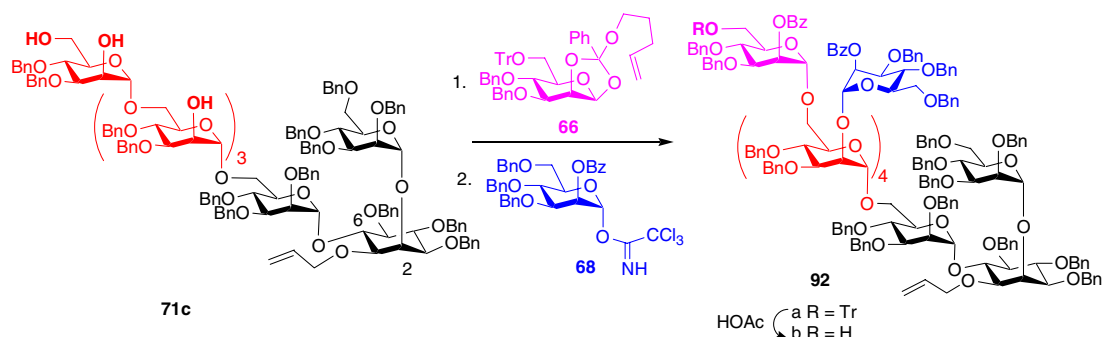
In view of the success of this diglycosidation of **83**, we tested a more elaborate donor. Our preliminary experiments taught us that branched NPG donors such as **84** were not reactive enough. A trichloroacetimidate was the obvious choice in view of the successes in Scheme 14, but as noted above, furanosides are extremely acid labile. It is therefore fortunate that the glycosidic *n*-pentenyl residue

can be cleaved oxidatively by treatment with NBS in aqueous medium. Trichloroacetimidation of the resulting glycoside could then proceed routinely to give **85**. Notably, disarmed donors, such as **85**, can be prepared and used at room temperature, whereas the armed counterparts do not survive at room temperature.

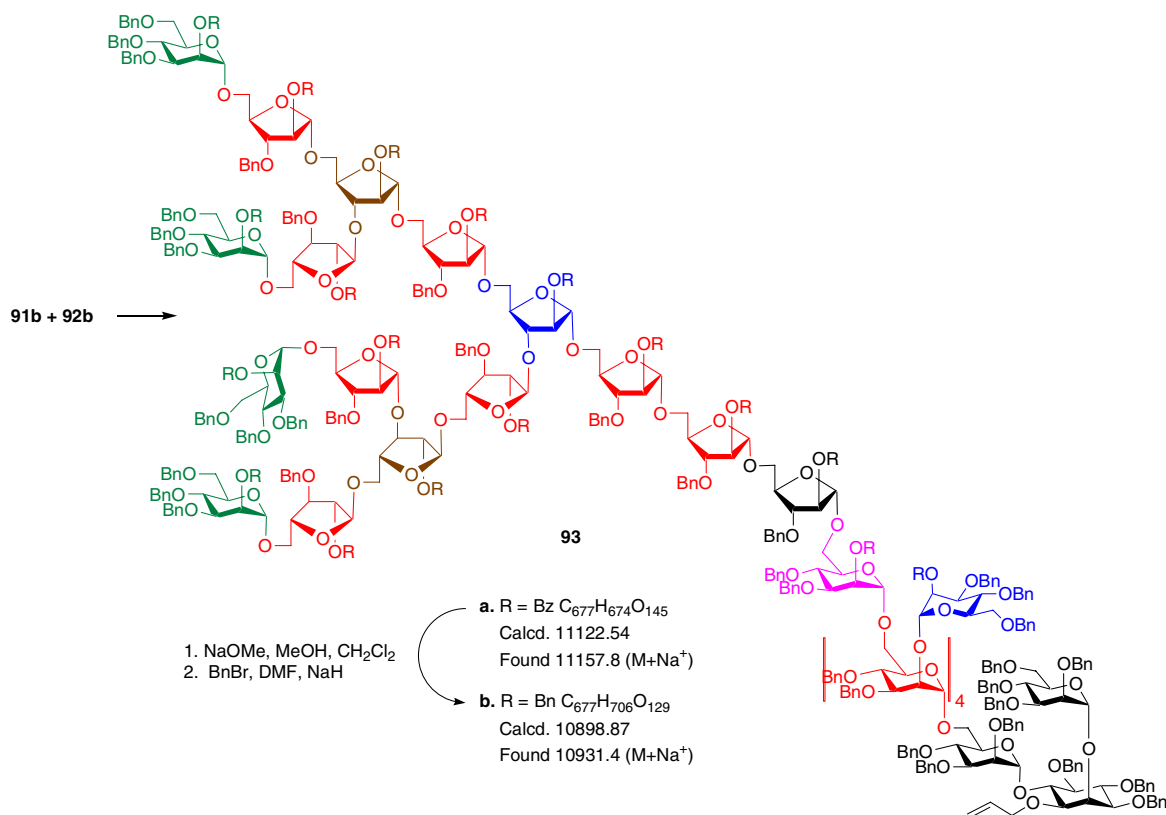
Unfortunately, when diol **83** was presented to 2 equiv of trichloroacetimidate **85**, the major product was **86**, there being very little double glycosidation. This suggested that the secondary-OH in **86** was too hindered for a complex donor like **85**. The contrast with the successful double glycosidation leading to **84**, taught us that a smaller donor, such as **76d**, must be used to achieve double glycosidation. In other words, double glycosidation would require two primary-OHs in the acceptor.⁶⁹

Accordingly, the linear trisaccharide **82** ($n = 1$) was converted into the tetrasaccharide diol **87** (Scheme 18), both hydroxyl groups of which were glycosidated with donor **77**, paving the way to hexafuranan **88** as the acceptor diol **89a** (Scheme 19).

For the donor partner, both hydroxyl groups of **79** were glycosidated with NPOE **77**, and desilylation gave product **89a**. In the above discussions of cartoons **60** and **61** (Scheme 10), we noted the importance of the mannose caps for biological activity in *M. tuberculosis*. Accordingly, the TBDMS group was removed, **89a** → **89b**, and mannosylation with excess NPOE **31**, afforded the mannose-capped *n*-pentenylated pentasaccharide **90a**, and routine processing then afforded trichloroacetimidate **90b**. Two equivalents of the latter now coupled readily with acceptor **88**



Scheme 20. Re-tooling the mannan array as an acceptor.



Scheme 21. Final assembly of the 28-mer oligosaccharide **93**.

affording hexadecasaccharide **91a** in 74% yield. The usual steps were then employed to prepare the trichloroacetimidate donor **91b**.

9. Donor 16 + Acceptor 12 = 28-mer

With the 16-mer donor **91b** in hand, we now had to return to **Scheme 14**, to prepare a modification of **72** to which the arabinan moiety, **91b**, could be attached. The primary-OH of its precursor, pentasaccharide **71c**, was covered by tritylation (**Scheme 20**), and the four secondary-OHs were then mannosylated, as in **Scheme 14**, to obtain **92a**. Detritylation then gave the desired dodecasaccharide acceptor **92b**.

Coupling of trichloroacetimidate **91b** with acceptor **92b** with $\text{Yb}(\text{OTf})_3$ gave ~60 mg of the 23-mer **93a** (**Scheme 21**) in 35% yield. The presence of 16 benzoate groups at all O2 sites on donor **91b** provided us with a ready method to validate product **93a**. Thus replacing all benzoates with benzyls would decrease the mass by 224. The mass spectroscopic data in **Scheme 21** is in accordance with this expectation.

10. Summary

Mannopyranose and arabinofuranose *n*-pentenyl orthoesters (NPOEs) are readily prepared from the parent sugars, and are easily converted into the related *n*-pentenyl glycosides and trichloroacetimidates. The latter donors and their NPOE progenitors are chemoselectively differentiated by $\text{Yb}(\text{OTf})_3$. In addition, the salt combines with *N*-iodosuccinimide to promote regioselective glycosidation of polyol acceptors by NPOEs, used in excess so as to optimize yields. These chemo- and regiopreferences provide a simple and reliable synthetic strategy that, additionally, is economical of time and materials. Thus the 12-mer mannan **91b** and 16-mer arabinan, **92b**, domains were assembled in 300 mg and 1 g quantities, respectively, each by one post-doctoral fellow in less than four weeks using conventional laboratory equipment, on the basis of considerable prior systematic research. The 28-mer **93** is, as far as we are aware of, the largest hetero-oligosaccharide that has been synthesized, slightly larger than Ogawa's 25-mer.⁷⁰

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