JOC Article

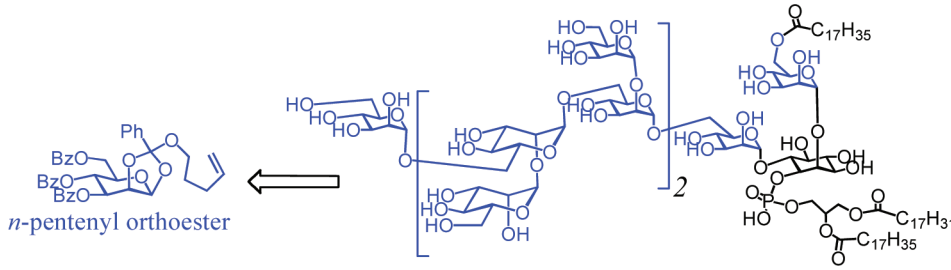
Efficient Chemical Synthesis of a Dodecasaccharidyl Lipomannan Component of Mycobacterial Lipoarabinomannan†

Bert Fraser-Reid,* Siddhartha Ray Chaudhuri, K. N. Jayaprakash,‡ Jun Lu,§ and Changalvala V. S. Ramamurty

Natural Products and Glycotechnology Research Institute, Inc., 595 F Weathersfield Road, Pittsboro, North Carolina 27312||

dglucose@aol.com

Received September 12, 2008



Lipomannan (LM) is one of the domains of lipoarabinomannan (LAM) glycolipids, the latter being one of several cell surface organic molecules that fortify mycobacterial species against external attack. Some members of mycobacterial families are pathogenic, most notably *Mycobacterium tuberculosis* and *Mycobacterium leprae*, while others are nonpathogenic, and used in the clinic, such as *Mycobacterium smegmatis*. Additional biological significance arises from the fact that LM has been implicated in several health disorders outside of those associated with mycobacterial pathogens, notably for treatment of bladder cancer. LM is comprised of a heavily lipidated phosphoinositide dimannoside headgroup, from which a mannan array, of varied complexity, extends. The latter consists of a 1,6-α-linked backbone flanked at position *O*2, not necessarily regularly, with α-linked mannosides. This paper gives an example of lipomannan synthesis in which all of the sugar components, whether functioning as donors or acceptors, are obtained from *n*-pentenyl orthoesters, themselves in turn prepared in three easy steps from D-mannose. Assembly of the mannan array is facilitated by the exquisite regioselectivity occasioned by the use of ytterbium triflate/*N*-iodosuccinimide as the trigger for reaction of *n*-pentenyl orthoesters.

Introduction

The newspaper reports[1] that a person with extensively drug resistant (XDR) tuberculosis[2] had been a passenger on airplanes in Europe, Canada, and the United States focused worldwide attention on the resurgence of tuberculosis.[3] This coverage achieved much more than Frank Ryan's riveting 1992 history "The Forgotten Plague"[4] about the return of the affliction once known as the Romantic Era Disease, the dire warnings of Reichman and Tanne[5] in their 2001 treatise entitled "Time Bomb", or Dormandy's "The White Death" with its thinly disguised allusions to the "black death" of the 15th century which killed one-third of Europe's population.[6]

* To whom correspondence should be addressed. Fax: 1-919-542-7111.

† Some parts of this work have been presented in preliminary communications in refs 43 and 67.

‡ Present address: Alnylam Pharmaceuticals, 300 3rd St, Cambridge, MA 02142.

§ Present address: Medtox, 1238 Anthony Road, Burlington, NC 27215.

|| An independent nonprofit research facility with laboratories at CiVentiCHEM, P.O. Box 12041, Research Triangle Park, NC 27709.

(1) (a) Altman, L. K.; Schwartz, J. *New York Times*; May 21, **2007**. (b) Altman, L. K. *New York Times*; June 1, **2007**.

(2) (a) Raviglione, M. C.; Smith, I. M. *New Engl. J. Med.* **2007**, *356*, 656–659. (b) Extensively drug-resistant tuberculosis—United States, 1993—2006. Centers for Disease Control and Prevention (CDC). *MMWR. Morbidity and mortality weekly report*, **2007**, *56*, 250—3.

(3) Consensus Statement. Global burden of tuberculosis: estimated incidence, prevalence and mortality by country W.H.O. Global Surveillance and Monitoring Project Dye, C.; Scheele, S.; Dolin, P.; Pathania, V.; Raviglione, M. C. *JAMA, J. Am. Med. Assoc.* **1999**, *282*, 677–686.

(4) Ryan, F. *The Forgotten Plague*; Little, Brown & Co.: Canada, 1992; p 415.

(5) Reichman, L. B.; Hopkins-Tanne, J. *Timebomb: The Global Epidemic of Multi-Drug-Resistant Tuberculosis*; McGraw-Hill: New York, 2001.

(6) Thomas Dormandy *The White Death*; New York University Press: New York, 2000.

10.1021/jo802000p CCC: $40.75 © 2008 American Chemical Society
Published on Web 11/07/2008

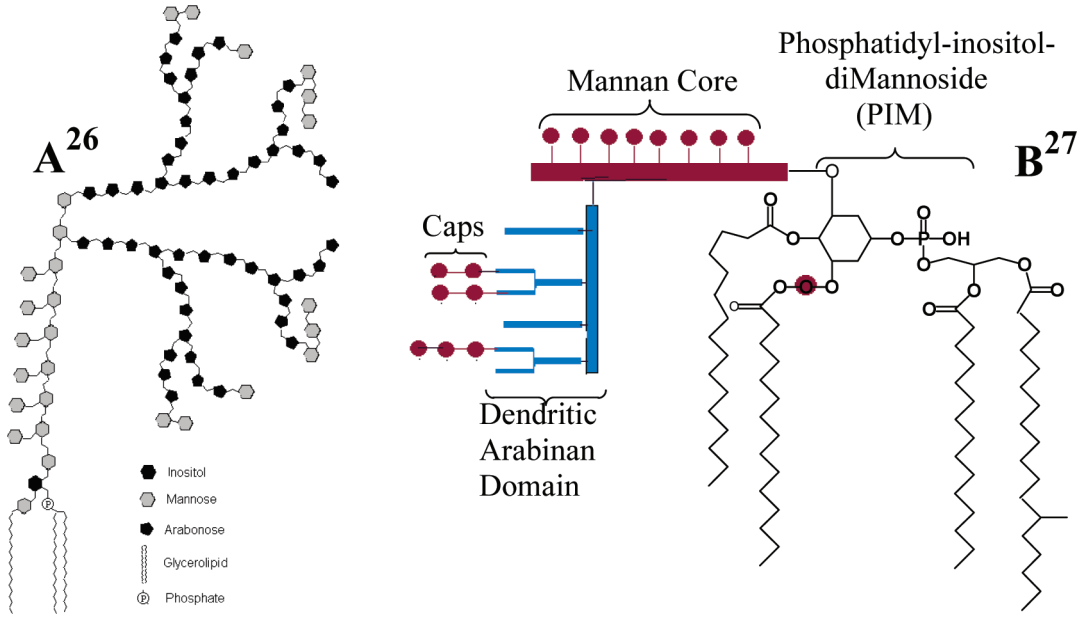


FIGURE 1. Cartoons of mycobacterial lipoarabinomannans (LAMs).[22,23]

Actually, the term "resurgence" may be apt for first-world nations, but not for many third-world countries where tuberculosis continues to be one of the most lethal bacterial diseases.[7,8] The disappearance of tuberculosis from first-world nations, a circumstance which is more apparent than real, is partly attributable to the rigorous regimen of multiple antibiotics that used to be administered ideally in sanatoria.[4,9] In less privileged nations, which lack facilities for such rigorous programs, treatment was incomplete, a consequence of which was the development of strains of the disease that are refractory to first line drugs. Thus, multiple drug resistant (MDR) tuberculosis[10] required expensive second line drugs such as kanamycin and amikasin. Not surprisingly, moderately drug resistant (MDR) tuberculosis was first noted in developing countries where early diagnosis and rigorous regimens are hard to maintain.[9] Added to this is the synergy with HIV, which enacts a woeful combination that has helped to transform MDR tuberculosis into extensively drug resistant tuberculosis (XDR),[2] a version that is proving resistant even to first line drugs such as isoniazid and rifampicin.[11]

Crowded environments such as prisons have provided convenient worldwide laboratories for studying the spread of tuberculosis. In view of data from such laboratories, antituberculosis medication is now being administered to some prison populations as a preemptive measure.[12]

The prospect is further clouded by the fact that one-third of the world's population is infected with *Mycobacterium tuberculosis*,[13] just waiting for an opportune time to become symptomatic.

The rigorous drug regimen administered to tuberculosis patients is, in part, demanded because of the extensive cell wall of organic chemicals that protects mycobacterial organisms from external agents.[14,15] A major component of this fortress is a massive polysaccharide estimated to contain dozens of sugar residues.[16,17] A contemporary nanoscale examination of these mycobacterial cell walls by atomic force microscopy correlates the action sites of the major antituberculosis drugs with their polysaccharide targets.[18] Thus, the target for ethambutol[19] is a major glycolipid subdomain known as lipoarabinomanan (LAM),[20] which is a major immunomodulatory agent.[21]

Challenges. LAM's multifaceted biological profile is matched by its multifaceted architecture. Two renditions of this architecture are captured in cartoons **A** and **B** (Figure 1) from the

(7) (a) Joe, M.; Bai, Y.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 9885–9901. (b) For a very recent summary, see: Thayer, A. *Chem. Eng. News* **2007**, *21*, and following.
(8) (a) Kapp, C. *Lancet* **2007**, *369* (9563), 729. (b) Gandhi, N. R.; Moll, A.; Sturm, A. W.; Pawinski, R.; Govender, T.; Lalloo, U.; Zeller, K.; Andrews, J.; Friedland, G. *Lancet* **2006**, *368* (9547), 1575–80.
(9) (a) Murray, J. F. *Bull. Int. Union Tuberc. Lung Dis.* **1991**, *66*, 199–204. (b) Brudney, K.; Dobkin, J. *Am. Rev. Respir. Dis.* **1991**, *144*, 746–749. (c) Sepkowitz, K. A.; Raffalli, J.; Riley, L.; Kiehn, D. *Am. Soc. Microbiol.* **1995**,
(10) Masjedi, M. R.; Famia, P.; Sorooch, S.; Pooramiri, M. V.; Mansoori, S. D.; Zarifi, A. Z.; AkbarVelayati, A.; Hoffner, S. *Clin. Infect. Dis.* **2006**, *43* (7), 841–847.
(11) (a) Caminero, J. A.; Pena, M. J.; Campos-Herreero, M. I.; Stead, W. W. *New Engl. J. Med.* **1999**, *341*, 1174–1179. (b) Cooper-Arnold, K.; Morse, T.; Pettigrew, C.; Hodgson, M.; Wallace, R.; Clive, J.; Gasecki, J. *Appl. Occup. Health Environ.* **2007**, *14*, 768–776.
(12) Caminero, J. A.; Pena, M. J.; Campos-Herrero, M. I.; Voelker, R.; et al. New Initiatives Target Inmates' Health. *JAMA, J. Am. Med. Assoc.* **2004**, *291* (13), 1549.
(13) Cummings, K. C.; Mohle-Boetani, J.; Royce, S. E.; Chin, D. P. *Am. J. Respir. Crit. Care Med.* **1998**, *157*, 1249–1252.
(14) For example, see: Brennan P. J. *Chem. Eng. News*; (Rouhi, A. M.) May 17, **1999**.
(15) (a) Bass, J. B., Jr.; Farer, L. S.; Hopewell, P.C.; Obriend, R.; Jacobs, R. F.; Ruben, F.; Snider, D. E.; Thornton, G. *Am. J. Respir. Crit. Care Med.* **1994**, *149*, 1359–1374. (b) Brennan, P. J. *Tuberculosis* **2003**, *83*, 91–87.
(16) Lowary, T. L. In *Mycobacterial Cell Wall Components in Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, 2001; pp 2005−2080.
(17) (a) Besra, G. S.; Khoo, K. H.; McNeil, M. R.; Dell, A.; Morris, H. R.; Brennan, P. J. *Biochemistry* **1995**, *34*, 4257. (b) McNeil, M. R.; Daffe, M.; Brennan, P. J. *J. Biol. Chem.* **1990**, *265*, 18200. (c) Lee, R. L.; Mikusova, K.; Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829.
(18) Alsteens, C. V.; Daague, E.; Raze, D.; Baulard, A. R.; Dufrene, Y. F. *Eur. J. Physiol.* **2008**, *456*, 117–125.
(19) (a) Deng, L. Y.; Mikusova, K.; Robuck, K. G.; Scherman, M.; Brennan, P. J.; McNeil, M. R. *Antimicrob. Agents Chemother.* **1995**, *39*, 694–701. (b) Mikusova, K.; Slayden, R. A.; Besra, G. S.; Brennan, P. J. *Antimicrob. Agents Chemother.* **1995**, *39*, 2484–2489. (c) Verbelen, C.; Dupre, V.; Menozzi, F. D.; Raze, D.; Baulard, A. R.; Hols, P.; Dufrene, Y. F. *FEMS Microbiol. Lett.* **2006**, *264*, 192–197.

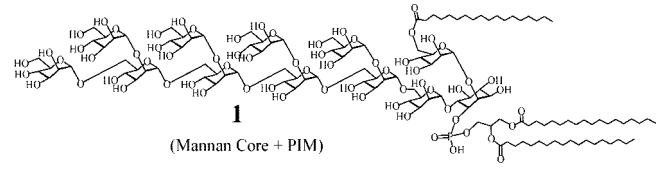
laboratories of Chatterjee, Puzo, and co-workers.[22,23] (Yet different representations are offered by Briken and co-workers[24]). The differences in these various representations reflect the daunting task faced by structural biologists to make confident assignments. The subunits, identified in cartoon **B**, are mannosylated phosphatidyl *myo*inositol (PIM), which is attached to the mannan array to give lipomannan (LM), which in turn is then attached to an arabinan complex, giving rise to LAM.[25] These subunits are major biosynthetic intermediates that are dispersed throughout mycobacterial cell walls and present valuable candidates for structure−activity studies.[26,27]

The dendritic arabinan domain, comprised of arabinofuranosyl components, is novel, and its challenging β-linked residues have engaged attention.[28] In this context, Lowary's recent syntheses of 18 and 22 residue arabinofurano dendrimers are noteworthy accomplishments.[29]

The so-called "caps" at the distal dendritic termini have been identified as seats of notable biological activity.[30]

A 28-mer construct consisting of dendritic arabinan and mannan/inositol domains, but lacking the crucial lipids, has recently been reported by our group.[31] However, lipidated constructs are of crucial importance, in view of the accumulating evidence of glycolipids in antigen presentation. The PIM subunit, where the lipids reside, has been a target of several laboratory syntheses.[32−34]

Attachment of the mannan core to PIM gives rise to LMs which are of independent biological interest in their own right.



1

(Mannan Core + PIM)

Thus, they exhibit "strong pro-inflammatory and apoptosis-inducing activity"[24,35] and have been implicated in a wide assortment of health disorders including herpes[36] and bladder cancer.[37] LM has even been found to potentiate HIV antiretrovials.[38]

Lipomannans are obtainable from nonmycobacterial sources,[39] and these naturally occurring sources have been a boon to biologists interested in structure−activity studies,[40] particularly in view of Nigou's belief that "synthesis of the LM portion (of LAM) (see Figure 1) can hardly be envisaged".[41,42] In spite of this discouraging prospect, after completing our synthesis of the triacylated phosphoinositide Ac_3PIM_2,[43] we conceived of compound **1** as a plausible construct of the lipomannan domain of cartoons **A** and **B**.

The aforementioned lack of confidence by Nigou and co-workers[41,42] in a laboratory route to LM undoubtedly arises from disillusionment with the standard protocol for synthesizing branched chained oligosaccharides, for which the strategy summarized in Scheme 1 is usually necessary.

Thus, the hydroxyl groups of **2** which are to be glycosylated must be differentially protected, for example, in precursor **4**, so as to allow each to be exposed independently, as in **5** and **7**, for presentation to each donor. The steps leading up to, and away from, the differentially protected intermediate **4** are as critical as the glycosylation steps themselves. However, protecting groups can alter saccharide reactivity as Paulsen showed 20 years ago,[44] and they can also influence glycosylation stereoselectivity[45−47] and even substrate conformation as Bols

(20) (a) Brennan, P. J. *Tuberculosis* **2003**, *83*, 91–97. (b) Guerardel, Y.; Maes, E.; Briken, V.; Chirat, F.; Leroy, Y.; Locht, C.; Strecker, G.; Kremer, L. *J. Biol. Chem.* **2003**, *278*, 36637–36651. (c) McNeil, M. R.; Robuck, K. G.; Harter, M.; Brennan, P. J. *Glycobiology* **1994**, *4*, 165–173. (d) Khoo, K. H.; Dell, A.; Morris, H. R.; Brennan, P. J.; Chatterjee, D. *J. Biol. Chem.* **1995**, *270*, 12380–12389. (e) Khoo, H. H.; Tang, J. B.; Chatterjee, D. *J. Biol. Chem.* **2001**, *276*, 3863–3871. (f) Prinzis, S.; Chatterjee, D.; Brennan, P. J. *J. Gen. Microbiol* **1993**, *139*, 2649–2658.

(21) (a) Chatterjee, D.; Khoo, K. H.; McNeil, M. R.; Dell, A.; Morris, H. R.; Brennan, P. J. *Glycobiology* **1993**, *3*, 497–506. (b) Venisse, A.; Berjeaud, J. M.; Chaurand, P.; Gilleron, M.; Puzo, G. *J. Biol. Chem.* **1993**, *268*, 12401–12411. (c) Chatterjee, D.; Lowell, K.; Rivoire, B.; McNeil, M. R.; Brennan, P. J. *J. Biol. Chem.* **1992**, *267*, 6234–6239. (d) Gilleron, M.; Himoudi, N.; Adam, O.; Constant, P.; Venisse, A.; Riviere, M.; Puzo, G. *J. Biol. Chem.* **1997**, *272*, 117–124. (e) Nigou, J.; Gilleron, M.; Puzo, G. *Biochimie (Paris)* **2003**, *85*, 153–166.

(22) Turnbull, W. B.; Shimizu, K. H.; Chatterjee, D.; Homans, S. W.; Trueman, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3918–3922.

(23) Riviere, M.; Moisand, A.; Lopez, A.; Puzo, G. *J. Mol. Biol.* **2004**, *344*, 907–915.

(24) Dao, D. N.; Kremer, L.; Guerardel, Y.; Molano, A.; Jacobs, W. R., Jr.; Porcelli, S. A.; Briken, V. *Infect. Immun.* **2004**, *72*, 2067–2074.

(25) Zhang, J.; Khoo, K.-H.; Wu, S.-W.; Chatterjee, D. *J. Am. Chem. Soc.* **2007**, *129*, 9650–9662, and references cited therein.

(26) (a) Maeda, N.; Nigou, J.; Hermann, I.; Jackson, M.; Amma, A.; Lagnange, P. H.; et al. *J. Biol. Chem.* **2003**, *278*, 5513–6. (b) Kremer, L.; Gurcha, S. S.; Bifani, P.; Hitchen, P. G.; Baulard, Al.; Morris, H. R.; Dell, A.; Brennan, P. J.; Besra, G. S. *Biochem. J.* **2002**, *3663*, 439.

(27) (a) Venisse, A.; Riviere, M.; Vercauteren, J.; Puzo, G. *J. Biol. Chem.* **1995**, *270*, 15012–15021. (b) Gilleron, M.; Nigou, J.; Cahuzac, B.; Puzo, G. *J. Mol. Biol.* **1999**, *285*, 2147–2160.

(28) (a) Zhu, X,; Kawatkar, S.; Rao, Y.; Boons, G.-J. *J. Am. Chem. Soc.* **2006**, *128*, 11948–11957. (b) Ishiwata, A.; Akao, H.; Ito, Y. *Org. Lett.* **2006**, *8*, 5525–5528. (c) Mereyala, H. B.; Hotha, S.; Gurjar, M. K. *Chem. Commun.* **1998**, 685–686. (d) D'Souza, F. W.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 1493–1495.

(29) (a) Rademacher, C.; Shoemaker, G. K.; Kim, H.-S.; Zheng, R. B.; Taha, H.; Liu, C.; Nacario, R. C.; Schriemer, D. C.; Klassen, J. S.; Peters, T.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 10489–10502. (b) Maju, J.; Yu, B.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 9885–9901.

(30) Nigou, J.; Gilleron, M.; Puzo, G. *Biochimie* **2003**, *85*, 153–166.

(31) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; Lopez, J. C. *Tetrahedron: Asymmetry* **2006**, *17*, 2449–2463.

(32) (a) Elie, C. J. J.; Verduyn, R.; Dreff, C. E.; Brounts, D. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1990**, *46*, 8243. (b) Elie, C. J. J.; Verduyn, R.; Dreff, C. E.; van der Marel, G. A.; van Boom, J. H. *J. Carbohydr. Chem.* **1992**, *11*, 715.

(33) (a) Hoelemann, A.; Stocker, B. L.; Seeberger, P. H. *J. Org. Chem.* **2006**, *71*, 8071–8088. (b) Liu, X.; Stoker, B. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 3638–3648.

(34) Completo, G. C.; Ponto, J. A.; Lowary, T. L. *J. Carbohydr. Chem.* **2005**, *24*, 517–527.

(35) Porcelli, S. A.; Besra, G. S. In *Intracellular Pathogens in Membrane Interactions Biogenesis*; Vacuole Gorvel, J. P., Ed.; Kluwer Academic Plenum Publishers: New York, 2004; pp 230−249.

(36) (a) Arkwright, P. D.; David, T. J. *J. Allergy Clin. Immunol.* **2001**, *107*, 531–534. (b) Kobayashi, M.; Herndon, D. N.; Pollard, R. B.; Suzuki, F. *Immunol. Lett.* **1994**, *40*, 199–205.

(37) (a) Young, S. I.; Murphy, M.; Zau, X. W.; Harnden, P.; O'Donnell, M. A.; James, K.; Patel, P. M.; Selby, P. J.; Jackson, A. M. *Int. J. Cancer* **2004**, *112*, 653–660. (b) Chin, J. L.; Salam, S. A.; Batislam, E.; Karlik, S. J.; Garcis, B. M.; Nickel, C.; Morales, A. *J. Urol.* **1996**, *156*, 1189–1193.

(38) Lesprit, P.; Zagdanski, A. M.; de la Blanchardiere, A.; Rouveau, M.; Decarpes, J. M.; Frija, J.; Lagrange, P.; Modai, J.; Molina, J. M. *Medicine* **1997**, *76*, 423–431.

(39) (a) Gibson, K. J. C.; Gilleron, M.; Constant, P.; Sichi, B.; Puzo, G.; Besra, G. S.; Nigou, J. *J. Biol. Chem.* **2005**, *280*, 28347–28356. (b) Lea-Smith, D. J.; Martin, K. L.; Pyke, J. S.; Tull, D.; McConville, J.; Coppel, R. L.; Crellin, P. K. *J. Biol. Chem.* **2008**, *283*, 6773–6782. (c) Ridgway, K. M.; Shi, W.; Lin, S.-J.; Palcic, M. M.; Lowary, T. L. *Can. J. Chem.* **2006**, *84*, 542–649.

(40) Maes, E.; Coddeville, B.; Kremer, L.; Guerardel, Y. *Glycoconjugate J.* **2007**, *24*, 439–448.

(41) Nigou, J. Power Point presentation at 28th Annual Meeting of Molecular Biology Society of Japan, 2005, entitled "Structure/function relationships of lipomannan as ligands of Toll-like receptor-2."

(42) Gibson, K. J. C.; Gilleron, M.; Constant, P.; Sichi, B.; Puzo, G.; Besra, G. S.; Nigou, J. *J. Biol. Chem.* **2005**, *280*, 28347–28356.

(43) Jayaprakash, K. N.; Lu, J.; Fraser-Reid, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3815–3819.

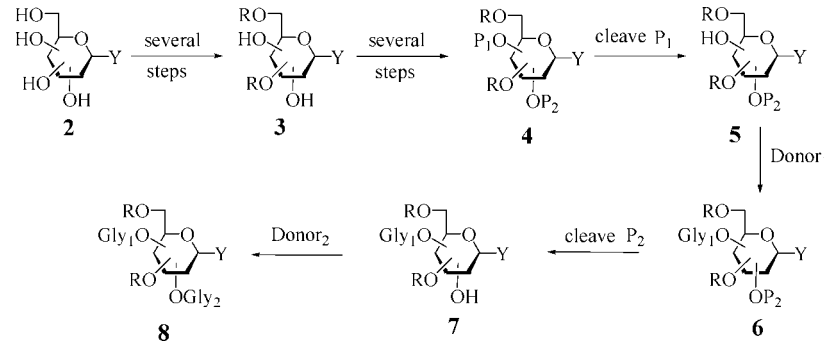
(44) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173.

(45) Crich, D. Stereocontrolled Glycosylations. In *Frontiers in Modern Carbohydrate Chemistry*; Demchenko, A. V., Ed.; ACS Symposium Series 960; American Chemical Society: Washington DC, 2007.

(46) Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215–3218.

(47) (a) Isbell, H. S. *Annu. Rev. Biochem.* **1940**, *9*, 65–92. (b) Frush, H. L.; Isbell, H. S. *J. Res. NBS* **1941**, *27*, 413.

SCHEME 1



and co-workers have recently shown.[48] As a result, the deployment of compatible, differential protecting groups required in **4** is the most demanding aspect of oligosaccharide preparation, indeed much more so than the glycosylation steps themselves.

Results and Discussion

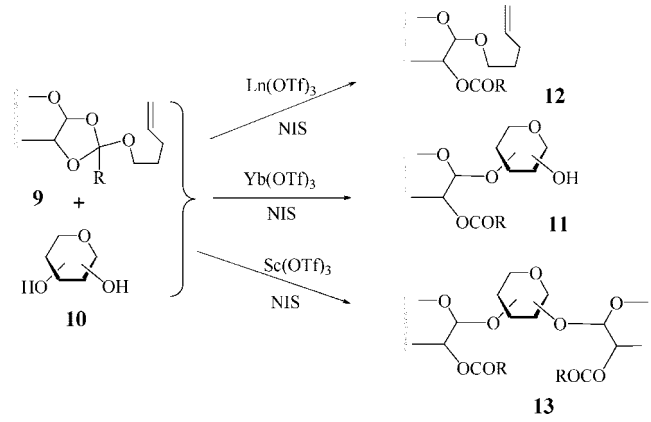
Issues of Regio- and Chemoselectivity. The demands of the processes in Scheme 1 could be reduced if regioselective glycosylation of acceptor polyols could be effected. That sugar-OH groups can sometimes be selectively protected, for example, by tritylation, silylation, and acylation, is well exemplified in the carbohydrate literature,[49] and it would seem logical to attempt to export such selectivities to the glycosylation process. However, this expectation is dispelled by several investigations. Thus, the random glycosylation studies in the laboratories of Hindsgaul[50] and Thiem[51] reveal that a sugar's primary-OH group is not necessarily the preferred site for glycosylation, as it is for affixing (most) protecting groups.

Studies in our laboratory have shown that it is possible to regioselectively glycosylate an acceptor polyol.[52] Thus, reaction of diol **10** with an *n*-pentenyl orthoester (NPOE) **9** in the presence of *N*-iodosuccinimide (NIS) gave the monoglycosylated product **11** when ytterbium triflate [$Yb(OTf)_3$] was used but the diglycosylated product **13** when scandium triflate [$Sc(OTf)_3$] was substituted (Scheme 2).

This selectivity results from the fact that Lewis acid catalyzed rearrangement of NPOE to disarmed NPG, **9**→**12**, occurs with many lanthanide triflates. However, ytterbium triflate/NIS does not activate **12**, whereas scandium triflate/NIS does.[53] An NPOE activated by NIS/$Yb(OTf)_3$ can therefore be used to effect chemoselective donor activation (e.g., between **9** and **12**) so as to achieve regioselective glycosidation of a polyhydroxylic acceptor.[54] This chemo/regioselectivity combination can therefore be relied upon to greatly simplify the process of branched-chain oligosaccharide assembly.[55]

The lipomannan **1** is an ideal candidate to test the chemo/regioselective advantages of the NPOE/$Ln(OTf)_3$ combination

SCHEME 2



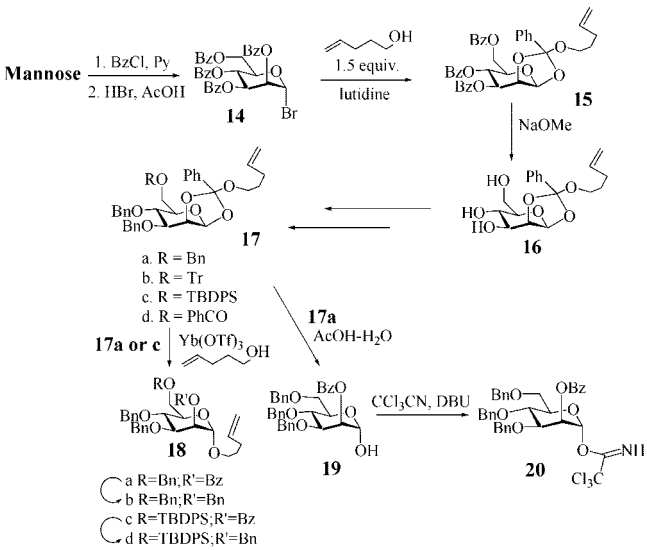
expressed in Scheme 2. The required manno-NPOE precursor **15** is prepared in three easy steps, requiring only 1.5 equiv of expensive *n*-pentenyl alcohol in the presence of lutidine, in the third step.[56] The triol **16** was converted into analogues **17a**−**d** using routine procedures.[57] Disarmed *n*-pentenyl glycosides, e.g., **18a**, can then be obtained by efficient rearrangement of the corresponding NPOE, e.g., **17a**, the armed analogue **18b** being then obtainable by routine methods.[57]

Hydrolysis of an NPOE, e.g., **17a** affords the glycose **19** from which the trichloroacetimidate **20** can be prepared routinely.[58] Access can therefore be had to a variety of donors of different reactivities, as well as with different requirements for activation.

The PIM Domain. The PIM domain of LAM (**1**, Figure 1) is a key biosynthetic precursor. Notably, all of the lipid residues, the number of which ranges from one to four,[59] are located there. A very recent publication by Dyer et al.[60] draws attention to some of the biological effects associated with the number of these acyl groups. McConville and co-workers, using cell free experiments with *Mycobacterium smegmatis*, have shown that acylation of the primary-OH of the mannoside located at inositol

(48) Pedersen, C. M.; Nordstro, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222–9236.
(49) (a) Sugihara, J. M. *Adv. Carbohydr. Chem.* **1953**, *8*, 1–44. (b) Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *3*, 11–109.
(50) Kanie, O.; Barresi, F.; Ding, Y.; Labbe, J.; Otter, A.; Forsberg, L. S.; Ernst, B.; Hindsgaul, O *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2720–2722.
(51) Steinmann, A.; Thimm, J.; Theim, J. *Eur. J. Org. Chem.* **2007**, 5506–5513.
(52) Jayaprakash, K. N.; Radhakrishnan, K. V.; Fraser-Reid, B. *Tetrahedron Lett.* **2002**, *43*, 6953–6955.
(53) Jayaprakash, K. N.; Fraser-Reid, B. *Synlett* **2004**, 301–305.
(54) Jayaprakash, K. N.; Fraser-Reid, B. *Org. Lett.* **2004**, *6*, 4211–4214.
(55) Jayaprakash, K. N.; Chaudhuri, S. R.; Murty Changalvala, V. S. R.; Fraser-Reid, B. *J. Org. Chem.* **2007**, *72*, 5534–5545.
(56) Lemieux, R. R.; Lineback, D. R. *Can. J. Chem.* **1965**, *43*, 94–105.
(57) Mach, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B. *Hazen Tetrahedron* **2002**, *58*, 7345–7354, K. C.
(58) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
(59) (a) Ainge, G. D.; Hudson, J.; Larsen, D. S.; Painter, G. F.; Gill, G. S.; Harper, J. L. *Bioorg. Med. Chem.* **2006**, *14*, 5632–5642. (b) Ainge, G. D.; Parlane, N. A.; Denis, M.; Hayman, C. M.; Larsen, D. S.; Painter, G. F. *Bioorg. Med. Chem.* **2006**, *14*, 7615–7624. (c) Sayers, G. D.; Severn, W.; Scanga, C. B.; Hudson, J.; le Gros, G.; Harper, J. L. *Allergy Clin. Immunol.* **2004**, *114*, 302–309.
(60) Dyer, B. S.; Jones, J. D.; Ainge, G. D.; Denis, M.; Larsen, D. S.; Painter, G. F. *J. Org. Chem.* **2007**, *72*, 3282–3288.
(61) Morita, Y. S.; Patterson, J. H.; Billman-Jacobe, H.; McConville, M. J. *Biochem. J.* **2004**, *378*, 537.

SCHEME 3



*O*2, "is an important step in regulating the size of" the PIMs, and that this acylation is "a mandatory step which precedes further mannosylation" at the inositol *O*6, resulting in the PIM pseudotrisaccharide.[61]

With respect to the inositol platform, differentially protected 2,6-diols, such as **21a** and **21b** (Scheme 4), are readily prepared by the biomimetic route of Bender and Budhu.[62] Such 2,6-diols were included among our test candidates in early mechanistic experiments[63] designed to probe Paulsen's concept of "match" in glycosidations.[64] Our investigations gave rise to the concept of reciprocal donor−acceptor selectivities (RDAS),[65] which reflects the fact that there is a *mutual* "match" between a donor and an acceptor-OH. For example when equivalent amounts of two donors, NPOE (**17a**) and armed NPG (**18b**), were forced to *compete* for a simultaneously presented acceptor diol, **21a**, (Scheme 4), a *single* pseudotrisaccharide was produced. Furthermore, only two pseudodisaccharides, **22** and **24**, were formed.[63,65] There was no evidence of the NPOE having reacted at O2-OH of **21a**, nor of the armed donor **18b** reacting at the *O*6-OH under these *competitive* conditions.

For the PIM component of **1** (Figure 1), the two mannosides on the inositol must be differentiated at the primary-OH positions. Since the primary-OHs can be easily liberated, the tritylated and silylated NPOEs **17b** and **17c** were logical candidates for O2 mannosylation of **21b**. However, in view of the above discussion relating to Scheme 2, it was necessary to evaluate the effect of lanthanide salts. In Scheme 5, 3 equiv of the NPOE donors, **17b/c**, were made available to the diol **21b**. With $Yb(OTf)_3$/NIS in Scheme 5a, mannosylation occurred exclusively at O6 to give **25a/b** in 97% and 92% yields, respectively. The excess donors were recovered as the disarmed NPGs **26a/b**. However, with $Sc(OTf)_3$/NIS, compounds **25a/b** were accompanied by substantial amounts of double glycosidation products, i.e., pseudotrisaccharides **27a/b**.

Formation of the latter most likely arose from O2 glycosidation of **25a/b** by the disarmed NPG, **26a/b**, produced by rearrangement of **17b/17c**.

Notably, with regard to the foregoing glycosidation, there is no inconsistency between Schemes 4 and 5b because in the latter there was no *competition* from an armed NPG. Indeed, as shown in Scheme 6, for efficient glycosidation of acceptor **25b** the armed NPG **18d** was used under the agency of scandium triflate and NIS. The 8:1 α/β mixture, **28**, obtained in 94% yield, was treated with sodium methoxide, whereupon chromatographic resolution took place affording the α,α product **29**. After benzylating the free-OH to obtain **30**, the primary-OH, required for growth of the mannan array, was freed by detritylation with TsOH. The anomeric configurations of **31** were confirmed by the carbon resonances at 99.15 and 98.24 ppm.[43]

The Lipomannan (LM) Domain. The next task was to elaborate the α-1,6-linked mannan chain which is the "backbone" of the lipomannan domain. Along this backbone are mannoside branches α-linked at O2 of each unit, and provision must therefore be made for this eventuality. The chemo- and regioselectivities that led from **10** → **11** (Scheme 2) could now be tested for elaborating the mannan domain.

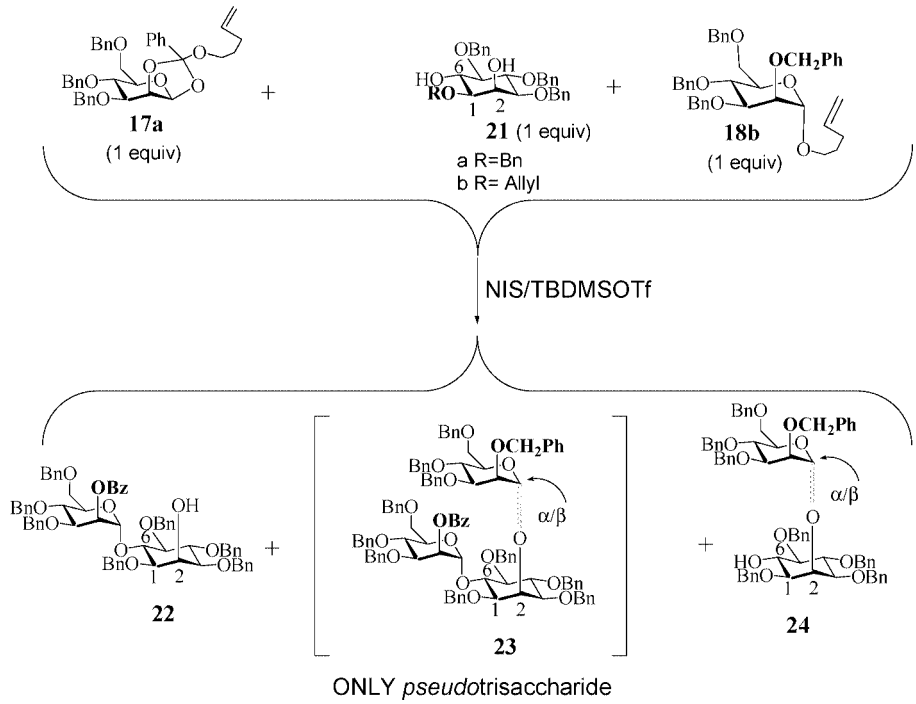
Thus, preliminary studies in our laboratory on lanthanide triflate/NIS activation of *n*-pentenyl donors[52−54] had shown that mannoside 2,6-diols, such as **32**, are cleanly glycosylated at the primary position when the ytterbium salt is used. For example, with donor **17a**, glycosylation of diol **32** gave product **33** exclusively (Scheme 7a). This regioselectivity is not merely an instance of normal primary versus secondary hydroxyl preference. Thus, in a timely, independent study, Lopez and coworkers[68] examined glycosylations of diols such as **34** and found that with NPOE **15** the exclusive monoglycosylated product was disaccharide **35** (Scheme 7b). By contrast, with the armed thioglycoside **36**, the preferred reaction occurred at O2, giving **37** as the major product (Scheme 7c). (Thioglycosides and *n*-pentenyl donors have been shown to exhibit parallel behaviors.[66])

In view of the results in Scheme 7a, a synthon for the 2,6-diol manno acceptor was required. NPOE **17d** is such a synthon because the O6 and O2 sites are protected, respectively, by formal and latent benzoates. Accordingly, pseudotrisaccharide acceptor **31** was glycosidated with an excess of NPOE **17d** under the agency of ytterbium triflate/NIS (Scheme 8). The crude product, **38a**, isolable in 97% yield, was directly saponified to obtain the pseudotetrasaccharide diol **38b** in 93% yield.

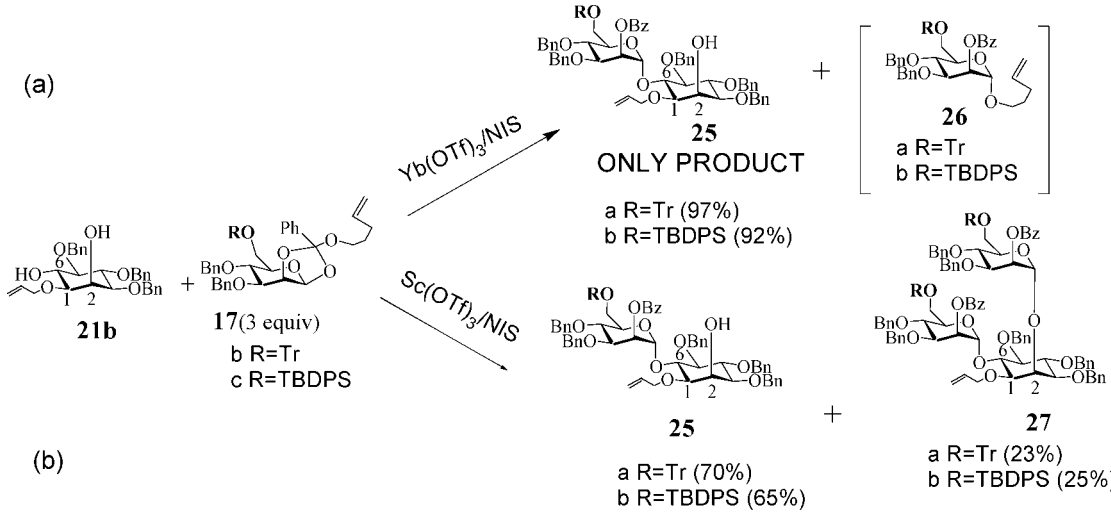
The success of the last two steps provided an encouraging approach to the backbone of **1**. Thus, beginning with diol **38b**, iteration of steps (i) and (ii) led to triol **39b**, tetraol **40b**, and pentaol **41b**, excellent yields between 85% and 93% being maintained as the system was lengthened.[67] The anomeric orientation of each newly introduced mannoside could be ascertained by studying the newly emerging signals in the carbon 13 spectrum. For example, in pseudotetrasaccharide **38b**, the three anomeric signals were seen at 99.44, 98.56, and 97.92 ppm. After one iteration to obtain pseudopentasaccharide **39b**, the four signals were at 100.10, 99.97, 99.02, 98.31 ppm, and

(62) Bender, S. L.; Budhu, R. J. *J. Am. Chem. Soc.* **1991**, *113*, 9883.
(63) Fraser-Reid, B.; López, J. C.; Radhakrishnan, K. V.; Mach, M.; Schlueter, U.; Gómez, A. M.; Uriel, C *Can. J. Chem.* **2002**, *124*, 1075–1087.
(64) Paulsen, H. In *Selectivity a Goal for Synthetic Efficiency*; Bartmann,W., Trost, B., Eds.; 1984.
(65) Fraser-Reid, B.; Lopez, J. C.; Gomez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, 1387–1395.
(66) Uriel, C.; Agocs, A.; Gómez, A. M.; López, J. C.; Fraser-Reid, B. *Org. Lett.* **2005**, *7*, 4899–4902.
(67) Jayaprakash, K. N.; Lu, J; Fraser-Reid, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5894–5898.
(68) Lopez, J. C.; Radhakrishnan, K. V.; Mach, M.; Schlueter, U.; Gomez, A.; Uriel, C. *J. Am. Chem. Soc.* **2002**, *124*, 3198–3199.
(69) (a) Yu, K. L.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979–982. (b) Campbell, A. S.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 10387–10388.
(70) Lu, J.; Jayaprakash, K. N.; Schlueter, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **2004**, *126*, 7540–7547.

SCHEME 4



SCHEME 5



after a further iteration to obtain pseudohexaasaccharide **40b**, the five signals were at 100.04, 100.03, 99.87, 99.07, 98.25 ppm. The final iteration leads to **41b**, where the six signals in question appear at 100.14, 100.12, 99.83, 99.72, 99.12, 98.24 ppm.

Completion of the mannan domain now required that all five hydroxyl groups of **41b** be mannosylated. Preliminary studies had shown that O2 hydroxyl groups of mannosides are glycosidated well with neither disarmed NPGs nor NPOE donors.[69] By contrast, we have found that disarmed trichloroacetimidates worked well.[54]

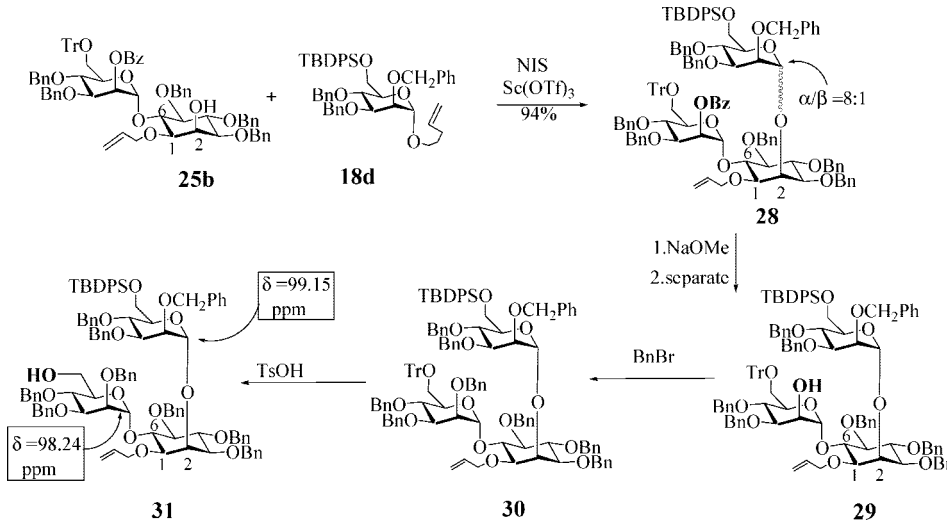
Accordingly, pentaol **41b** was exhaustively glycosidated, using a 2-fold molar excess of trichloroacetimidate **20**, this having been previously prepared from the corresponding NPOE progenitor **17a** as outlined in Scheme 3.

Lipidation. The benzoate groups in the resulting dodecasaccharide **42a** were removed (**42b**) and replaced with benzyls (**42c**) so that installation of the lipid entities could begin.

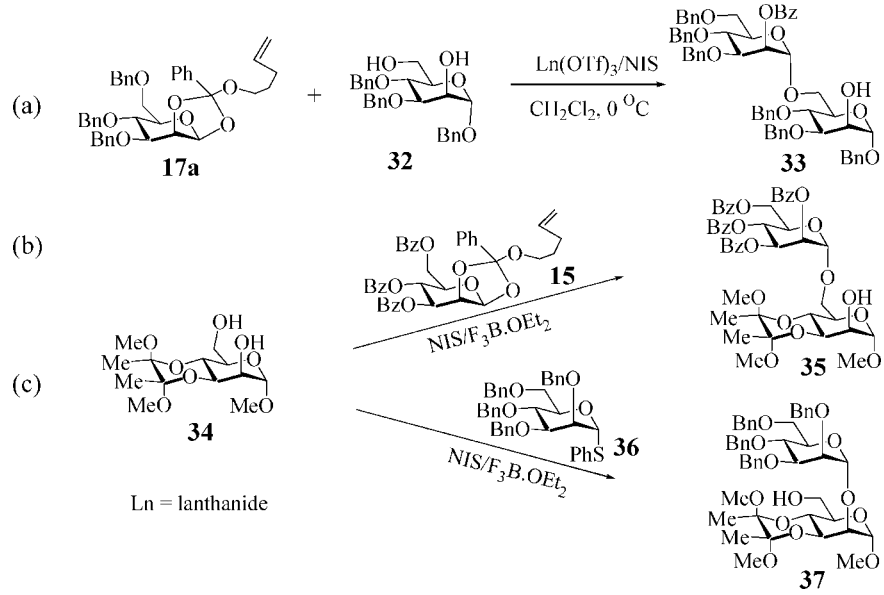
Desilylation of pseudododecassacharide **42c** liberated the primary hydroxyl, and the resulting product, **43a**, was acylated routinely with stearoyl chloride to obtain the 6-*O*-lipidated mannoside **43b**, in 88% yield. The allyl protecting group was removed by treatment with palladium chloride in aqueous acetic acid, product **44** being recovered in the moderate yield of 65%. For the final phospholipidation, we relied on our standard protocol,[69] in which the diacylated phosphoramidite, **45**, is installed under the agency of tetrazole, followed by oxidation. A 75% yield of the triester **46** was thereby obtained.

Hydrogenolysis. The final step was to remove the benzyl protecting groups while ensuring that the three acyl groups remained intact. Use of chloroform/methanol mixtures with palladium hydroxide and hydrogen at 50 psi, effected efficient cleavage of the benzyl groups, but unfortunately, the acyl groups did not survive. Palladium hydroxide was therefore replaced[70] with 10% palladium on carbon with chloroform/methanol (1:

SCHEME 6



SCHEME 7



1) mixture, but under these conditions there was only partial debenzylation and the substrate tended to "oil" out. The latter result indicated that a more polar solvent mixture was required. Inclusion of water in a chloroform/methanol/water (3:3:1) mixture provided a suitable medium, debenzylation being effected without event in 3 h.

Conclusions

n-Penytenyl orthoesters (NPOEs) are versatile structures that have enabled synthesis of the lipomannan **1**. Obtainable in three easy steps from D-mannose, NPOE **15** is readily converted into other donors, such as disarmed and armed NPGs, as well as to trichloroacetimidates. The different activation demands of these various donors permit skeptical choices for glycosidations because of their nuanced reactivities. A given NPOE can therefore serve readily as a synthon for other donors as well as for acceptors. Thus, all 11 mannoside residues of **1** emanate from a single source, NPOE **15**. The partnership between NPOEs and ytterbium triflate/*N*-iodosuccinimide affords exquisite regioselectivity in glycosylation of polyols, fulfilling of the concept of "match" in reactions of donors and acceptors.

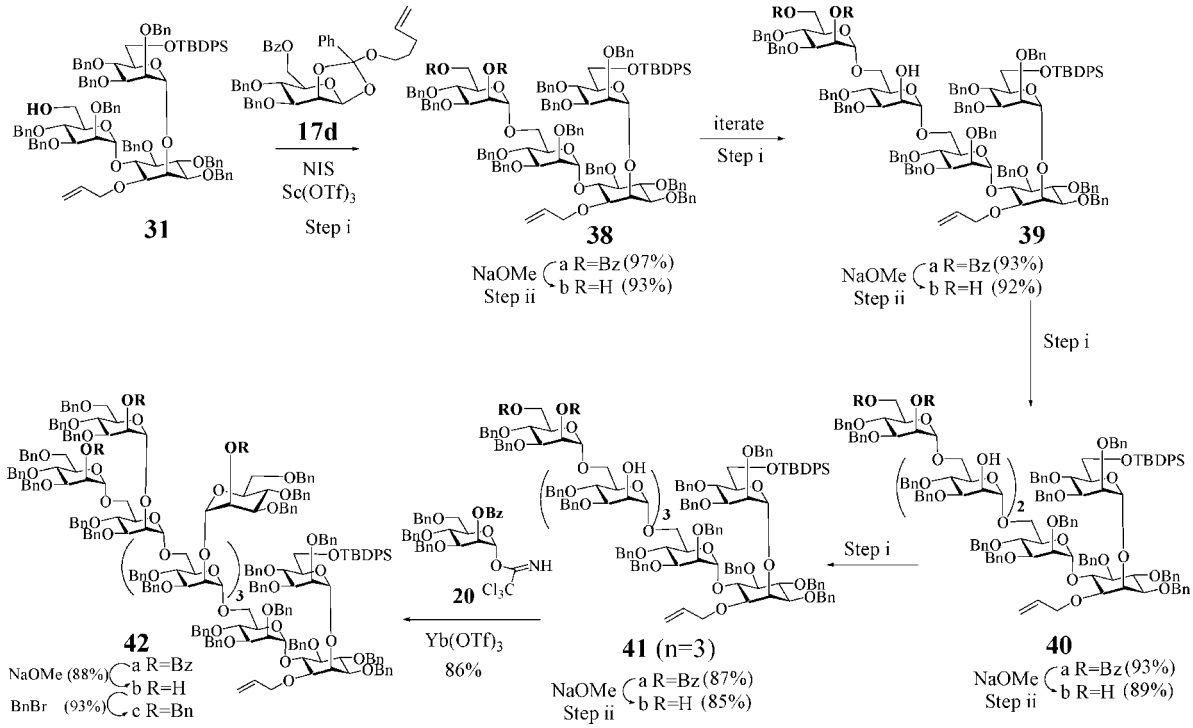
Experimental Section

The β-D-mannopyranose 1,2-(pent-4-enyl orthobenzoates) [*n*-pentenyl orthoesters (NPOEs)], **17a**−**d**, armed NPG **18**, mannosyl trichloroacetimidates **20**, and the myoinositol derivative **21** were prepared as described previously.[43,54,57,62]

General Glycosidation Conditions. The acceptor (1 equiv) and donor (3 equiv) were dissolved separately in a small quantity of toluene, azeotroped to dryness, and kept overnight under vacuum. The acceptor was dissolved in dry CH_2Cl_2 (5−10 mL) at 0 °C under argon atmosphere, NIS (3−4 equiv) was added, and after stirring for 5 min, the Lewis acid or lanthanide triflate (0.3 equiv) was also added. The donor was dissolved in CH_2Cl_2 (10 mL) and added dropwise over a period of 15−30 min until TLC indicated completion. The reaction was quenched with 10% aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate, extracted with CH_2Cl_2, and purified by chromatography.

(2-*O*-Benzoyl-3,4-di-*O*-benzyl-6-*O*-triphenylmethyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol

SCHEME 8



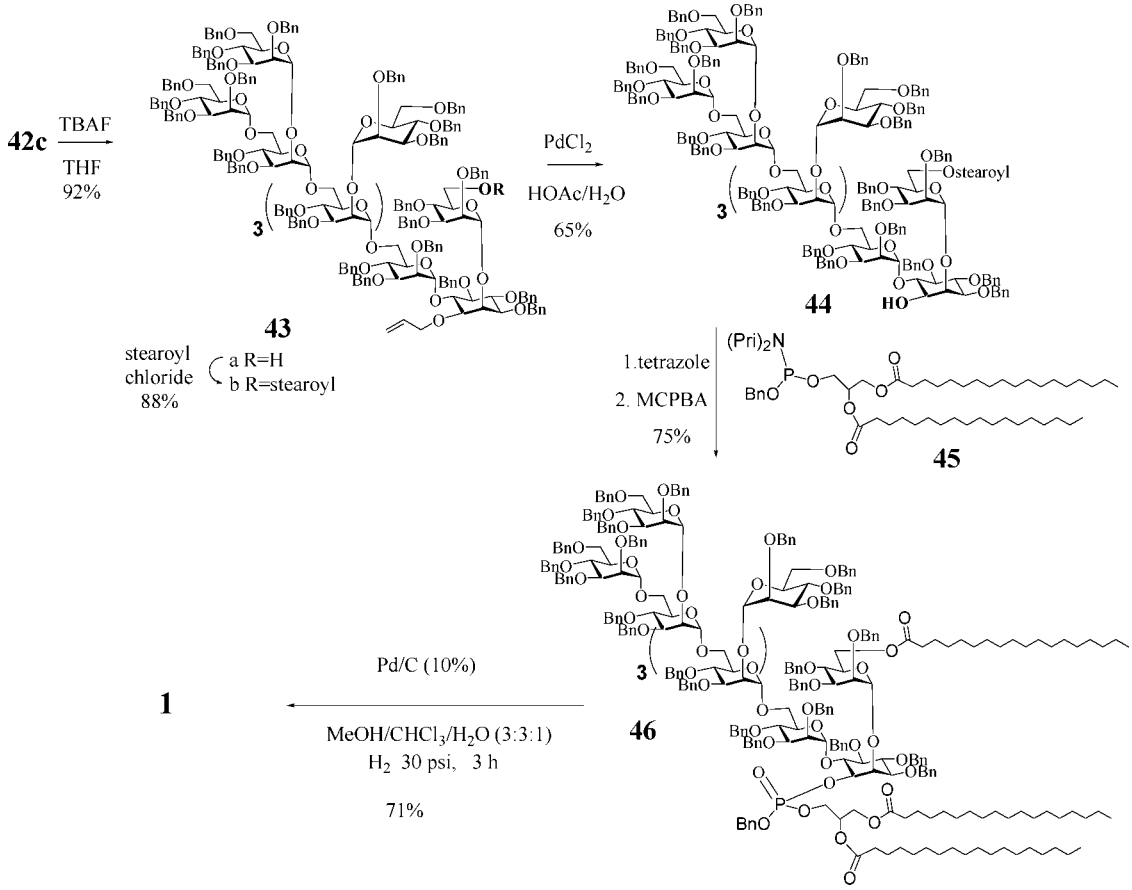
(25a). The acceptor **21b** (0.50 g, 1.02 mmol) and the donor **17b** (2.33 g, 3.06 mmol) were coupled using NIS (0.685 g, 3.06 mmol) and $Yb(OTf)_3$ (0.190 g, 0.30 mmol) in 8 mL of CH_2Cl_2 using the general procedure (gradient elution 5−25% EtOAc/hexanes) to give **25a** (1.15 g, 97%). Separation from the accompanying disarmed donor **26** was uneventful. **25a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 7.8 Hz, 2H), 7.57 - 6.79 (m, 43H), 6.03 - 5.98 (m, 1H), 5.75 (dd, J = 1.8, 2.7 Hz, 1H), 5.61 (d, J = 1.8 Hz, 1H), 5.34 - 5.20 (m, 2H), 4.91 - 3.98 (m, 19H), 3.44 - 3.29 (m, 3H), 2.85 (m, 1H), 2.43 (BS, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.68, 144.10, 138.54, 138.35, 138.11, 137.69, 134.12, 132.84, 130.14, 129.78, 129.64, 128.71, 128.35, 128.17, 128.12, 127.84, 127.77, 127.74, 127.72, 127.60, 127.41, 127.36, 127.15, 126.95, 126.90, 126.55, 118.38, 98.51, 85.87, 81.20, 80.97, 80.44, 79.66, 78.22, 75.83, 75.75, 75.15, 72.69, 71.62, 71.35, 69.46, 66.70, 62.06; MS calcd 1178.52, found 1201.9 (M + Na^+).

(2,3,4-Tri-*O*-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-triphenylmethyl-α,β-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (28). Acceptor **25a** (1.046 g, 0.884 mmol) and the armed donor **18d** (2.00 g, 3 equiv) were dissolved together in small amount of toluene, azeotroped to dryness, and kept under vacuum overnight. The mixture was dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C. NIS (0.800 g, 4 equiv) was added, and the mixture was stirred stirred for 5 min followed by the addition of $Sc(OTf)_3$ (0.131 g, 0.3 equiv). The mixture was stirred for 0.5 h, checked by TLC, and quenched with satd sodium bicarbonate and 10% sodium thiosulfate solutions. The organic layer was extracted with CH_2Cl_2 and dried over Na_2SO_4. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (gradient elution 5−15% ethyl acetate in hexane) to obtain the unresolved 8:1 mixture **28** (1.54 g, 94%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 7.5 Hz, 2H), 6.92−7.64 (m, 64H), 6.01 (m, 1H), 5.89 (dd, J = 1.5, 2.8 Hz, 1H), 5.60 (d, J = 1.5 Hz, 1H), 5.27−5.41 (m, 3H), 3.00−5.09 (m, 35H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 166.00, 144.48, 139.36, 138.90, 138.70, 138.60, 138.47, 138.10, 137.88, 136.39, 135.93, 134.37, 134.24, 133.42, 130.55, 130.26, 129.71, 129.12, 128.91, 128.81, 128.66, 128.56, 128.51, 128.46, 128.43, 128.35, 128.31, 128.20, 128.06, 128.02, 127.85, 127.78, 127.74, 127.64, 127.49, 127.35, 127.03, 119.09, 99.40, 98.28, 86.29, 81.78, 81.68, 81.50, 79.16, 78.71, 77.55, 75.99, 75.84, 75.61, 75.42, 74.82, 74.66, 72.95, 72.79, 72.47, 72.09, 71.92, 69.99, 69.80, 63.05, 62.60, 60.78, 27.27, 19.83; MS for $C_{119}H_{120}O_{17}Si$ calcd 1853.30, found 1873.8 (M + Na).

(2,3,4-Tri-*O*-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-α,β-D-mannopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-6-*O*-triphenylmethyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (29). The trisaccharide mixture **28** (1.54 g, 0.831 mmol) was dissolved in CH_2Cl_2/CH_3OH mixture and treated with excess of NaOMe (0.5 M solution in MeOH). The mixture was stirred for 2 days at room temperature to complete the debenzoylation (TLC). Solvents were removed, and the residue was extracted with CH_2Cl_2 and saturated ammonium chloride solution and dried over Na_2SO_4. Dichloromethane was removed under reduced pressure, and the residue was purified by chromatography to get the desired product [(1.353 g, 93%, 1.09 g of **29** (α,α) and 0.263 g of the (α,β) counterpart]. For **29** (α,α): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, J = 7.00 Hz, 2H), 7.690 (d, J = 7.00 Hz, 2H), 6.92−7.54 (m, 61H), 5.82 (m, 1H), 5.58 (d, J = 1.5 Hz, 1H), 5.27−5.38 (m, 3H), 3.00−5.05 (m, 36H), 2.52 (d, J = 3.00 Hz, 1H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.34, 139.35, 138.79, 138.73, 138.66, 138.59, 138.41, 138.26, 137.91, 136.35, 135.91, 134.16, 133.94, 129.68, 129.60, 129.09, 128.74, 128.60, 128.56, 128.51, 128.46, 128.40, 128.25, 128.22, 128.13, 127.93, 127.81, 127.75, 127.65, 127.60, 127.51, 127.46, 127.31, 126.97, 118.40, 99.85, 98.29, 86.29, 82.24, 81.91, 81.54, 80.49, 79.17, 75.98, 75.74, 75.52, 75.19, 74.65, 72.95, 72.57, 72.53, 72.02, 71.63, 71.52, 69.75, 69.33, 63.06, 62.54, 27.25, 19.78; MS for $C_{112}H_{116}O_{16}Si$ calcd 1746.20, found 1769.8 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(2,3,4-tri-*O*-benzyl-6-*O*-triphenylmethyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (30). The trisaccharide **29** (1.405 g, 0.805 mmol) was dissolved in ∼20 mL of dry DMF and cooled to 0 °C, NaH (0.065 g, 2 equiv) was added, and the mixture was stirred for 0.5 h. Benzyl bromide (0.158 mL, 1.5 equiv) and a catalytic amount of TBAI were added, and the reaction mixture was stirred at 0 °C for another

SCHEME 9



1 h. TLC was checked, and the reaction mixture was quenched with water. The mixture was extracted with ether and brine and dried over Na_2SO_4. Solvents were removed, and the residue was purified by chromatography to obtain compound **30** (1.450 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 7.8 Hz, 2H), 7.67 (d, J = 7.8 Hz, 2H), 6.85−7.50 (m, 66H), 5.79 (m, 1H), 5.57 (d, J = 1.5 Hz, 1H), 5.16−5.32 (m, 3H), 2.91−5.00 (m, 38H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.64, 139.40, 139.18, 139.10, 138.97, 138.72, 138.35, 138.01, 136.44, 136.01, 134.35, 134.25, 134.04, 129.80, 129.25, 128.63, 128.52, 128.33, 128.26, 128.09, 128.01, 127.95, 127.81, 127.71, 127.58, 127.41, 126.99, 118.26, 99.21, 98.45, 86.29, 82.35, 82.00, 81.57, 80.42, 79.43, 79.33, 77.37, 76.91, 76.41, 76.06, 75.86, 75.63, 75.29, 74.76, 73.11, 72.90, 72.70, 72.50, 72.32, 71.23, 69.68, 63.18, 62.69, 27.36, 19.89; MS for $C_{119}H_{122}O_{16}Si$ calcd 1836.32, found 1858.7 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (31). The trisaccharide **30** (1.417 g, 0.771 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (20 mL) and treated with PTSA (1 equiv). The reaction mixture was stirred for 4 h (TLC) and then quenched with triethylamine. Solvents were removed, and the residue was purified by chromatography to give **31** (1.16 g, 94%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, J = 7.8 Hz, 2H), 7.69 (d, J = 7.8 Hz, 2H), 7.01−7.47 (m, 51H), 5.80 (m, 1H), 5.52 (d, J = 1.5 Hz, 1H), 5.35 (s, 1H), 5.20−5.29 (m, 2H), 3.23−5.00 (m, 32H), 1.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.21, 139.10, 138.89, 138.82, 138.69, 138.58, 138.13, 137.85, 136.31, 135.90, 134.18, 134.10, 133.88, 129.92, 129.71, 129.62, 128.82, 128.68, 128.57, 128.50, 128.42, 128.31, 128.21, 128.09, 127.83, 127.73, 127.62, 127.49, 127.33, 118.23, 99.15, 98.24, 82.16, 81.71, 80.32, 79.55, 79.28, 741.42, 76.02, 75.87, 75.70, 75.59, 75.41, 75.01, 74.74, 73.07, 72.96, 72.81, 72.60, 72.40, 71.07, 69.36, 63.11, 62.00, 27.24, 19.78; MS for $C_{100}H_{108}O_{16}Si$ calcd 1594.00, found 1617.0 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(2,6-di-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (38a). The acceptor **31** (1.10 g, 0.688 mmol) and the donor **17d** (1.31 g, 3 equiv) were dissolved in a small amount of toluene, azeotroped to dryness, and kept under vacuum overnight. The mixture was then dissolved in 20 mL of CH_2Cl_2 and cooled to −5 °C, and NIS (0.619 g, 4 equiv) was added. The reaction mixture was stirred for a few minutes, $Sc(OTf)_3$ (0.102 g, 0.3 equiv) was introduced, and the mixture was stirred at −5 °C for 2 h. TLC was checked, and the reaction was quenched with satd sodium bicarbonate and 10% sodium thiosulfate solutions. The organic layer was extracted into CH_2Cl_2 and dried over Na_2SO_4. Solvents were removed under reduced pressure, and the residue was purified by column chromatography to obtain the desired tetrasaccharide dibenzoate **38a** (1.44 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.0 Hz, 4H), 7.73 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.56−7.50 (m, 2H), 7.43−6.90 (m, 65H), 5.79 (t, J = 2.8 Hz, 1H), 5.75−5.64 (m, 1H), 5.47 (s, 1H), 5.28−3.17 (m, 51H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.97, 165.06, 138.93, 138.87, 138.56, 138.52, 138.49, 138.27, 138.17, 138.04, 137.90, 137.50, 135.94, 135.53, 133.83, 133.72, 133.52, 132.77, 130.18, 129.99, 129.73, 129.54, 129.34, 129.25, 128.54, 128.30, 128.22, 128.20, 128.08, 127.90, 127.57, 127.52, 127.45, 127.44, 127.38, 127.24, 126.96, 117.78, 98.54, 98.10, 97.88, 81.56, 81.27, 81.14, 80.26, 78.95, 78.86, 77.20, 75.67, 75.15, 75.20, 75.05, 74.93, 74.69, 74.22, 73.09, 72.60, 72.25, 71.87, 71.12, 70.77, 70.55, 69.64, 68.80, 68.30, 65.71, 62.87, 62.66, 26.70, 19.19; MS for $C_{134}H_{138}O_{23}Si$ calcd 2144.60, found 2170.2 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (38b). The dibenzoate **38a** was dissolved in a CH_2Cl_2/MeOH mixture and treated with excess NaOMe (0.5

M solution in MeOH) overnight at room temperature. Solvents were removed, and the residue extracted with CH_2Cl_2 and satd ammonium chloride solution. Solvents were removed, and the residue was purified by chromatography to give **38b** (1.23 g, 93%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.40−6.92 (m, 61H), 5.80−5.68 (m, 1H), 5.43 (s, 1H), 5.26−5.09 (m, 4H), 5.00−3.14 (m, 48H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.88, 138.78, 138.55, 138.48, 138.39, 138.30, 138.14, 137.83, 137.57, 137.46, 135.91, 135.51, 133.79, 133.67, 133.50, 129.79, 129.67, 129.57, 128.69, 128.57, 128.53, 128.48, 128.44, 128.36, 128.29, 128.24, 128.06, 128.01, 127.90, 127.79, 127.63, 127.61, 127.45, 127.27, 117.79, 99.44, 98.56, 97.92, 81.65, 81.21, 81.11, 80.10, 78.96, 78.88, 78.83, 75.71, 75.51, 75.06, 74.78, 74.67, 74.21, 74.14, 73.70, 72.58, 72.48, 72.36, 72.18, 71.95, 71.86, 71.52, 71.23, 71.14, 70.61, 68.91, 67.74, 65.20, 62.62, 61.57, 26.68, 19.16; MS for $C_{120}H_{130}O_{21}Si$ calcd 1936.39, found 1961.7 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,6-di-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (39a). The tetrasaccharide **38b** (1.214 g, 0.625 mmol) and the donor **17d** (1.195 g, 3 equiv) were dissolved separately in two different flasks in small amounts of toluene and evaporated to dryness. The flasks were kept under vacuum overnight. The acceptor **38b** was dissolved in 10 mL of CH_2Cl_2 and cooled to 0 °C, NIS (0.422 g, 3equiv) and $Yb(OTf)_3$ (0.116 g, 0.3 equiv) were introduced, and the mixture was stirred for a few minutes. The donor **17d** was dissolved in CH_2Cl_2 and added dropwise over a period of 15 min to the reaction mixture. After complete disappearance of acceptor (TLC), the reaction was worked up in the usual way and the residue was purified by chromatography to give desired compound **39a** (1.45 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.2 Hz, 4H), 7.77 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 7.5 Hz, 2H), 7.50−7.59 (m, 2H), 6.97−7.45 (m, 75H), 5.78 (dd, J = 1.8, 3.00 Hz, 1H), 5.77 (m, 1H), 5.49 (d, J = 1.6 Hz, 1H), 5.29 (s, 2H), 5.13−5.25 (m, 2H), 3.22−5.05 (m, 52H), 2.40 (bs, 1H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.29, 165.52, 139.26, 139.17, 138.82, 138.61, 138.45, 138.27, 137.92, 127.84, 136.27, 135.86, 134.14, 134.08, 133.86, 133.35, 133.22, 133.13, 130.41, 130.22, 130.12, 129.88, 129.06, 129.56, 128.70, 128.68, 128.61, 128.56, 128.47, 128.44, 128.41, 128.33, 128.26, 128.16, 128.01, 127.90, 127.80, 127.75, 127.65, 127.58, 127.49, 127.43, 127.28, 127.20, 118.14, 100.16, 99.06, 98.65, 98.24, 82.05, 81.67, 81.53, 80.65, 79.80, 79.42, 79.25, 78.17, 77.92, 76.07, 75.97, 75.52, 75.46, 75.08, 74.99, 74.72, 74.61, 73.87, 73.73, 73.01, 72.80, 72.72, 72.45, 72.35, 71.93, 71.78, 71.50, 71.33, 71.05, 70.93, 70.39, 70.21, 69.55, 69.07, 68.98, 67.91, 66.31, 66.18, 63.60, 63.48, 63.13, 27.21,19.76; MS for $C_{154}H_{160}O_{28}Si$ calcd 2486.99, found 2512.6 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (39b). The dibenzoate **39a** (1.45 g, 0.582 mmol) was debenzoylated under the usual conditions to obtain the compound **39b** (1.217 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 6.9 Hz, 2H), 7.73 (d, J = 6.9 Hz, 2H), 7.02−7.50 (m, 71H), 5.81 (m, 1H), 5.55 (s, 1H), 5.35 (s, 2H), 5.18−5.30 (m, 2H), 3.25−5.10 (m, 53H), 2.74 (bs, 1H), 2.30 (bs, 1H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.26, 139.20, 138.90, 138.80, 138.71, 138.51, 138.30, 138.06, 137.86, 136.32, 135.92, 134.18, 134.10, 133.90, 129.73, 129.63, 128.78, 128.60, 128.53, 128.48, 128.44, 128.39, 128.32, 128.28, 128.15, 127.96, 127.86, 127.80, 127.71, 127.62, 127.49, 127.33, 118.21, 100.10, 99.97, 99.02, 98.31, 82.13, 81.72, 81.61, 80.68, 79.72, 79.43, 79.30, 77.88, 77.45, 77.03, 76.05, 75.59, 75.42, 75.05, 74.75, 74.60, 74.30, 73.86, 73.04, 72.88, 72.73, 72.42, 72.13, 71.91, 71.53, 71.10, 70.83, 69.20, 68.42, 68.00, 65.99, 63.14, 62.19, 27.26, 19.78; MS for $C_{140}H_{152}O_{26}Si$ calcd 2278.77, found 2303.6 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,6-di-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (40a). The pentasaccharide triol **39b** (1.216 g, 0.533 mmol), donor **17d** (1.107 g, 3 equiv), NIS (0.360 g, 3 equiv), and $Yb(OTf)_3$ (0.099 g, 0.3 equiv) were treated under the glycosidation conditions described for **38a** to give the hexasaccharide dibenzoate **40a** (1.405 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 7.2 Hz, 2H), 7.82 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 7.8 Hz, 2H), 7.50−7.59 (m, 2H), 7.00−7.45 (m, 85H), 5.83 (dd, J = 1.6, 3.00 Hz, 1H), 5.79 (m, 1H), 5.54 (s, 1H), 5.35 (s, 1H), 3.25−5.21 (m, 72H), 2.57 (bs, 1H), 2.25 (bs, 1H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.34, 165.65, 139.28, 139.17, 138.91, 138.84, 138.76, 138.71, 138.51, 138.32, 138.28, 138.110, 137.97, 137.88, 136.32, 135.92, 134.19, 134.11, 133.91, 133.31, 133.18, 130.42, 130.17, 129.92, 129.72, 129.62, 128.78, 128.61, 128.53, 128.44, 128.31, 128.14, 127.96, 127.86, 127.79, 127.70, 127.64, 127.49, 127.34, 127.28, 118.18, 100.41, 100.09, 99.09, 98.61, 98.32, 82.12, 81.72, 81.60, 80.67, 80.09, 79.87, 79.49, 79.31, 77.96, 77.28, 76.03, 75.51, 75.24, 75.01, 74.77, 74.59, 73.87, 73.77, 73.06, 72.88, 72.75, 72.50, 72.42, 71.84, 71.56, 71.47, 71.09, 70.62, 70.28, 69.66, 69.13, 68.12, 67.99, 66.47, 66.09, 63.54, 63.16, 27.26, 19.78; MS for $C_{174}H_{182}O_{33}Si$ calcd 2829.37, found 2856.4 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (40b). Compound **40a** (1.40 g, 0.494 mmol) was debenzoylated under the conditions described earlier to get compound **40b** (1.153 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 2H), 7.68 (d, J = 7.5 Hz, 2H), 6.97−7.44 (m, 81H), 5.79 (m, 1H), 5.50 (s, 1H), 5.31 (s, 2H), 5.14−5.29 (m, 2H), 3.21−5.65 (m, 70H), 2.80 (bs, 1H), 2.42 (bs, 1H), 2.28 (bs, 1H), 1.09 (s, 9H);.^{13}C NMR (75 MHz, $CDCl_3$) δ 139.24, 139.17, 138.91, 138.87, 138.80, 138.78, 138.68, 138.66, 138.49, 138.29, 138.08, 137.96, 137.83, 137.81, 136.27, 135.88, 134.14, 134.08, 133.88, 129.67, 129.57, 128.72, 128.57, 128.48, 128.46, 128.41, 128.36, 128.31, 128.27, 128.25, 128.19, 128.13, 128.09, 127.92, 127.87, 127.81, 127.75, 127.71, 127.65, 127.58, 127.46, 127.39, 129.31, 118.51, 100.04, 100.03, 99.87, 99.07, 98.25, 82.05, 81.69, 81.56, 80.60, 80.12, 79.75, 79.39, 79.26, 76.18, 76.00, 75.53, 75.40, 75.18, 74.98, 74.73, 74.61, 74.33, 74.06, 73.91, 70.03, 72.86, 72.72, 72.46, 72.40, 72.14, 71.94, 71.44, 71.05, 70.79, 70.68, 69.11, 68.42, 68.13, 67.96, 66.37, 66.18, 65.98, 63.13, 62.22, 27.22, 19.75; MS for $C_{160}H_{174}O_{31}Si$ calcd. 2621.60, found 2647.2 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,6-di-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (41a). The hexasaccharide **40b** (0.526 g, 0.200 mmol), donor **17d** (0.381 g, 3 equiv), NIS (0.135 g, 3 equiv), and $Yb(OTf)_3$(0.037 g. 0.3 equiv) were treated under the glycosidation conditions described previously to get the heptasaccharide dibenzoate **41a** (0.360 g, 87% recovered **40b**, 180 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 7.80 Hz, 4H), 7.81 (d, J = 7.2 Hz, 2H), 7.70 (d, J = 7.2 Hz, 2H), 7.55−7.62 (m, 2H), 6.97−7.46 (m, 95H), 5.80 (dd, J = 1.80, 3.00 Hz, 1H), 5.78 (m, 1H), 5.51 (s, 1H), 5.31 (s, 2H), 3.21−5.25 (m, 85H), 2.61 (bs, 1H), 2.36 (bs, 1H), 2.22 (bs, 1H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.31, 165.65, 139.28, 139.16, 138.92, 138.85, 138.80, 138.74, 138.71, 138.53, 138.30, 138.13, 137.99, 137.86, 136.28, 135.89, 134.17, 134.13, 133.25, 133.13, 130.45, 130.26, 130.14, 129.90, 129.67, 129.57, 128.73, 128.58, 128.55,

128.50, 128.45, 128.41, 128.39, 128.34, 128.25, 128.15, 128.09, 127.92, 127.90, 127.81, 127.77, 127.66, 127.59, 127.50, 127.39, 127.34, 118.15, 100.27, 100.08, 99.11, 98.55, 98.28, 82.10, 81.76, 81.58, 80.60, 80.15, 80.07, 79.83, 79.46, 79.30, 78.02, 76.20, 76.10, 75.99, 75.47, 75.23, 75.12, 75.05, 74.98, 74.77, 74.64, 74.10, 73.83, 73.12, 73.05, 72.89, 72.76, 72.50, 72.43, 72.04, 71.94, 71.86, 71.57, 71.47, 71.18, 71.08, 71.92, 70.74, 70.30, 69.17, 68.18, 68.01, 66.56, 66.15, 63.57, 63.19, 27.36, 19.98; MS for $C_{194}H_{204}O_{38}Si$ calcd 3171.76, found 3195.3 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (41b). Compound **41a** (0.355 g g, 0.120 mmol) was debenzoylated under the usual conditions to get compound **41b** (0.280 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 2H), 7.66 (d, J = 7.8 Hz, 2H), 6.96−7.45 (m, 91H), 5.78 (m, 1H), 5.49 (s, 1H), 5.30 (s, 2H), 5.04−5.27 (m, 2H), 3.20−4.96 (m, 84H), 2.40 (bs, 5H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.25, 139.16, 138.89, 138.88, 138.82, 138.69, 138.66, 138.60, 138.50, 138.30, 138.14, 137.99, 137.92, 137.83, 136.26, 135.86, 134.14, 134.10, 133.88, 129.65, 129.55, 128.73, 128.71, 128.56, 128.53, 128.49, 128.47, 128.44, 128.38, 128.32, 128.24, 128.13, 128.05, 127.90, 127.86, 127.79, 127.75, 127.63, 127.56, 127.43, 127.37, 127.31, 125.51, 118.12, 100.14, 100.12, 99.83, 99.72, 99.12, 98.24, 82.04, 81.74, 81.54, 80.56, 80.12, 79.833, 79.76, 79.43, 79.27, 76.19, 76.08, 75.96, 75.49, 75.40, 75.17, 75.12, 75.05, 74.99, 74.75, 74.63, 74.40, 74.24, 74.14, 73.93, 73.09, 73.03, 72.88, 72.73, 72.48, 72.41, 72.16, 71.98, 71.41, 71.05, 70.85, 70.73, 70.65, 69.09, 68.43, 68.15, 67.97, 66.57, 66.43, 66.21, 66.05, 63.15, 62.28, 27.22, 19.73; MS for $C_{180}H_{196}O_{36}Si$ calcd 2963.55, found 2987.0 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-{2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,6-di-*O*-benzoyl-3,4,-di-*O*-benzyl-α-D-mannopyranosyl}-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (42a). The heptasaccharide pentaol **41b** (0.279 g, 0.094 mmol) and mannosyl trichloroacetimidate donor **20** (0.642 g, 10 equiv) were dissolved in a small amount of toluene and evaporated to dryness. The mixture was dried under vacuum for about 4 h and dissolved in 15 mL of dry ether. Molecular sieves were added, the reaction mixture was cooled to 0 °C, and triethylsilyl triflate(50 μL) was added. The mixture was stirred for 10 min, checked by TLC, and quenched with triethylamine. The reaction mixture was filtered and purified by chromatography gave the dodecasaccharide **42a** (0.461 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02−8.11 (m, 10H), 7.77 (d, J = 6.9 Hz, 2H), 7.67 (d, J = 7.5 Hz, 2H), 7.51−7.57 (m, 5H), 6.99−7.44 (m, 176H), 5.83 (dd, J = 1.6, 3.60 Hz, 1H), 5.79 (dd, J = 1.8, 3.00 Hz, 2H), 5.75 (dd, J = 1.8, 3.00 Hz, 1H), 5.72 (m, 1H), 5.67 (dd, J = 1.8, 3.00 Hz, 1H), 5.43 (s, 1H), 5.14−5.24 (m, 5H), 3.02−5.10 (m, 139H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.58, 165.49, 165.45, 139.31, 139.08, 139.04, 138.95, 138.86, 138.80, 138.76, 138.57, 138.50, 138.41, 138.05, 137.93, 137.90, 137.86, 137.74, 136.33, 135.94, 134.22, 134.10, 133.90, 133.19, 130.42, 130.29, 130.23, 129.76, 129.67, 129.32, 128.90, 128.74, 128.60, 128.59, 128.53, 128.43, 128.39, 128.31, 128.25, 128.14, 128.06, 128.02, 127.97, 127.90, 127.81, 127.72, 127.68, 127.65, 127.62, 127.56, 127.47, 127.38, 127.18, 127.08, 126.99, 126.96, 126.89, 126.89, 118.18, 100.08, 99.72, 99.62, 99.56, 99.40, 98.42, 81.88, 81.62, 81.04, 80.44, 80.05, 79.86, 79.60, 79.33, 79.23, 79.17, 79.11, 78.94, 78.12, 77.90, 76.04, 75.63, 75.44, 75.27, 75.08, 74.80, 74.64, 74.27, 73.98, 73.86, 73.77, 73.60, 73.20, 72.83, 72.70, 72.62, 72.20, 72.05, 71.88, 71.71, 71.50, 71.39, 71.26, 71.09, 70.82, 70.62, 70.52, 70.38, 69.40, 69.23, 68.98, 68.86, 67.67, 66.80, 66.61, 65.87, 69.97, 64.75, 63.19, 60.79, 27.29, 19.80; MS for $C_{350}H_{356}O_{66}Si$ calcd 5642.43, found 5667.7 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{3,4-di-*O*-benzyl-α-D-mannopyranosyl}-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (42b). The dodecasaccharide **42a** (0.460 g, 0.081 mmol) was dissolved in CH_2Cl_2/CH_3OH and treated with sodium methoxide (excess) for 2 days to remove all the benzoate groups. The reaction was worked in the usual way to obtain the desired compound **42b** (0.371, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 6.8 Hz, 2H), 7.69 (d, J = 6.8 Hz, 2H), 6.94−7.47 (m, 166H), 5.80 (m, 1H), 5.54 (s, 1H), 3.11−5.32 (m, 151H), 3.01 (d, J = 10.4 Hz, 2H), 2.77 (bs, 1H), 2.55 (bs, 1H), 2.49 (bs, 2H), 2.44 (bs, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.28, 139.24, 138.96, 138.87, 138.83, 138.76, 138.73, 138.62, 138.57, 138.48, 138.36, 138.10, 138.01, 137.91, 137.85, 137.70, 137.67, 136.27, 135.89, 134.17, 134.06, 133.85, 130.20, 129.70, 129.60, 128.67, 128.53, 128.42, 128.35, 128.28, 128.23, 128.08, 127.97, 127.84, 127.77, 127.72, 127.63, 127.47, 127.34, 127.12, 126.86, 126.77, 126.73, 118.16, 102.13, 101.91, 101.74, 101.29, 100.28, 99.54, 99.32, 98.85, 98.23, 81.84, 81.58, 81.00, 80.85, 80.66, 80.58, 79.88, 79.72, 79.52, 79.27, 78.89, 76.78, 76.46, 76..02, 75.66, 75.54, 75.41, 75.25, 75.18, 74.61, 74.48, 73.92, 73.69, 73.58, 73.54, 73.18, 73.07, 72.85, 72.79, 72.43, 72.33, 72.16, 71.94, 71.76, 71.54, 71.19, 71.00, 70.74, 70.51, 70.31, 69.16, 68.80, 68.04, 66.54, 64.52, 63.16, 27.23, 19.75; MS for $C_{315}H_{336}O_{61}Si$ calcd 5126.09, found 5155.3 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranosyl)-(1→2)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (42c). The pentaol **42b** (0.520 g, 0.102 mmol) was exhaustively benzylated by dissolving in DMF (6 mL). After the mixture was cooled to 0 °C, NaH (0.040 g, 10 equiv) was added and stirred for 0.5 h. Benzyl bromide (100 μL) and TBAI (20 mg) were introduced, and stirring was maintained at 0 °C for 1 h. TLC was checked, and workup yielded compound **42c** (0.525 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.01−7.48 (m, 191H), 5.80 (m, 1H), 5.56 (s, 1H), 3.20−5.34 (m, 161H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.29, 139.11, 138.92, 138.79, 138.61, 138.57, 138.38, 138.21, 137.89, 137.76, 137.65, 137.56, 136.31, 135.92, 134.22, 134.10, 133.89, 129.73, 129.63, 128.76, 128.62, 128.50, 128.47, 128.38, 128.33, 128.30, 128.20, 128.15, 127.99, 127.87, 127.81, 127.77, 127.71, 127.65, 127.59, 127.52, 127.37, 127.24, 127.01, 126.91, 126.71, 118.15, 100.10, 99.93, 99.75, 99.47, 98.75, 98.36, 81.95, 81.79, 81.59, 80.97, 80.80, 80.59, 80.36, 79.97, 79.71, 79.64, 79.30, 78.18, 76.56, 76.00, 75.57, 75.38, 75.26, 75.12, 74.83, 74.63, 74.39, 74.05, 73.61, 73.20, 73.16, 72.84, 72.47, 72.37, 72.19, 72.06, 71.45, 71.07, 70.70, 70.55, 69.45, 69.23, 69.08, 66.78, 66.02, 65.59, 63.19, 27.27, 19.78; MS for $C_{350}H_{366}O_{61}Si$ calcd 5576.70, found 5602.8 (M + Na).

(2,3,4-tTri-*O*-benzyl-α-D-mannopyranosyl)-(1→2)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (43a). The dodecasaccharide **42c** (0.520 g, 0.093 mmol) was dissolved in dry THF (10 mL), and molecular seives were

added followed by TBAF (1 mL in THF). The mixture was stirred for 24 h to give the desilylated compound **43a** (0.456 g, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08−7.48 (m, 185H), 5.80 (m, 1H), 5.55 (s, 1H), 3.15−5.32 (m, 161H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.31, 139.17, 138.99, 138.95, 138.90, 138.84, 138.78, 138.65, 138.60, 138.40, 138.24, 138.09, 137.92, 137.79, 137.66, 137.58, 129.20, 128.83, 128.70, 128.55, 128.39, 128.27, 128.06, 127.83, 127.71, 127.26, 127.02, 126.92, 126.73, 118.03, 100.06, 99.88, 99.72, 99.44, 99.35, 98.71, 81.81, 81.49, 80.98, 80.77, 80.54, 80.33, 79.65, 79.34, 78.95, 78.01, 76.16, 76.01, 75.78, 75.64, 75.43, 75.24, 75.11, 75.02, 74.85, 74.55, 74.39, 74.26, 74.11, 74.01, 73.93, 73.57, 73.52, 73.10, 72.92, 72.81, 72.73, 72.52, 72.45, 72.39, 72.34, 72.06, 71.99, 71.84, 71.45, 71.36, 71.22, 71.07, 70.71, 70.56, 70.43, 70.33, 69.33, 69.12, 68.89, 69.99, 66.82, 66.43, 66.54, 65.94, 62.37; MS for $C_{334}H_{398}O_{61}$ calcd 5334.41, found 5356.8 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-stearoyl-(1→2)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-myoinositol (43b). The dodecasaccharide **43a** (0.450 g, 0.084 mmol) was dissolved in pyridine/CH_2Cl_2(1:2) and treated with stearoyl chloride (0.051 g, 2 equiv) and DMAP (20 mg). The mixture was stirred overnight, solvents were removed, and the residue was purified by chromatography to give the desired compound **43b** (0.415 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05−7.47 (m, 185H), 5.80 (m, 1H), 5.52 (s, 1H), 3.18−5.29 (m, 160H), 2.33 (t, 7.5 Hz, 2H), 1.90 (m, 2H), 1.31−1.36 (m, 33H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.82, 139.23, 139.11, 138.90, 138.84, 138.80, 138.78, 138.73, 138.66, 138.63, 138.57, 138.52, 138.47, 138.34, 138.22, 137.91, 137.78, 137.66, 137.57, 134.10, 128.87, 128.75, 128.62, 128.56, 128.47, 128.38, 128.33, 128.29, 128.23, 128.20, 128.14, 127.98, 127.81, 127.77, 127.71, 127.65, 127.63, 127.59, 127.53, 127.25, 127.01, 126.92, 126.71, 126.73, 118.01, 100.12, 99.93, 99.76, 99.56, 98.96, 98.77, 81.85, 81.52, 81.01, 80.80, 80.59, 80.37, 79.74, 79.28, 78.79, 78.17, 76.19, 76.02, 75.84, 75.54, 75.43, 75.25, 75.12, 74.92, 74.62, 74.40, 74.23, 74.07, 73.61, 73.16, 72.83, 72.47, 72.37, 72.19, 72.06, 71.91, 71.59, 71.47, 71.37, 71.17, 70.84, 70.72, 70.55, 69.46, 69.23, 69.04, 66.97, 66.81, 66.49, 66.03, 63.37, 39.66, 32.37, 30.15, 30.11, 30.07, 29.95, 29.82, 29.71, 29.65, 25.32, 23.16; MS for $C_{352}H_{382}O_{62}$ calcd 5600.67, found 5625.3 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-stearoyl-(1→2)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-3,4,5-tri-*O*-benzyl-D-myoinositol (44). Compound **43b** (0.385 g, 0.069 mmol) was dissolved in AcOH (5 mL), and water (0.250 mL) was added. The mixture was treated with NaOAc (0.034 g, 6 equiv) and $PdCl_2$ (0.037 g, 3 equiv) and stirred at rt for 2 days. TLC was checked, and the reaction was worked up under normal conditions to give **44** (0.250 g, 65%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02−7.48 (m, 185H), 5.60 (s, 1H), 5.20−5.28 (m, 5H), 3.14−5.07 (m, 151H), 2.17 (t, J = 7.2 Hz, 2H),1.90 (m, 2H), 1.2−1.37 (m, 33H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.98, 139.13, 138.96, 138.85, 138.75, 138.71, 138.60, 138.56, 138.51, 138.40, 138.37, 138.21, 138.18, 137.96, 137.77, 137.68, 128.86, 128.74, 128.71, 128.67, 128.61, 128.54, 128.51, 128.37, 128.363, 128.27, 128.24, 128.19, 128.12, 128.04, 128.01, 127.94, 127.89, 127.83, 127.79, 127.77, 127.73, 127.66, 127.63, 127.52, 127.31, 127.25, 126.85, 126.76, 100.16, 100.04, 99.97, 99.90, 99.95, 98.65, 81.61, 81.03, 80.68, 80.54, 80.48, 80.30, 80.13, 79.97, 79.61, 79.20, 78.60, 78.24, 77.53, 77.22, 76.90, 75.81, 75.59, 75.51, 75.20, 75.14, 75.09, 74.82, 74.65, 74.55, 74.36, 74.08, 73.77, 73.56, 73.49, 73.45, 73.40, 73.04, 72.77, 72.64, 72.39, 72.33, 72.26, 72.12, 72.03, 71.93, 71.34, 71.16, 70.86, 70.57, 70.45, 70.27, 69.33, 69.20, 68.86, 67.97, 67.44, 67.21, 66.72, 65.95, 63.53, 34.33, 32.23, 30.02, 29.97, 29.94, 29.81, 29.68, 29.59, 29.48, 25.10, 23.01; MS for $C_{349}H_{378}O_{62}$ calcd 5560.64, found 5583.6 (M + Na).

(2,3,4-Tri-*O*-benzyl-6-*O*-stearoyl-(1→2)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl}-(3,4-di-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-{2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl}-(2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→63,4,5-tri-*O*-benzyl)-1-*O*-(1,2-di-*O*-stearoyl-sn-glycero-3-benzylphosphoryl)-D-myoinositol (46). To a solution of **39** (56 mg, 0.01 mmol) and glycerylphosphoramidite **40** (41 mg, 0.05 mmol) in CH_2Cl_2/CH_3CN (2:1, 3 mL) was added tetrazole (7 mg, 0.1 mmol). The solution was stirred at rt for 5 h. After the reaction was completed, the reaction mixture was cooled to−20 °C, and *m*-CPBA (15 mg, 0.05 mmol) was added. The reaction mixture was stirred at this temperature for 1 h. Saturated $Na_2S_2O_3$ solution was added to quench the reaction. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was washed with aq $NaHCO_3$ and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (hexane/EtOAc/Et_3N 3:1:0.01) to give compound **46** (47 mg, 75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.87−7.38 (m, 195 H), 5.40 (s, 1 H), 3.57−5.22 (m, 71 H), 2.98−3.45 (m, 17 H), 2.13−2.37 (m, 6H), 1.42−1.78 (m, 6H), 1.05−1.26 (m, 90 H), 0.98 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.44, 172.97, 172.62, 139.10, 138.92, 138.74, 138.69, 138.63, 138.61, 138.57, 138.51, 138.42, 138.35, 138.12, 138.00, 137.80, 137.71, 137.60, 137.55, 137.49, 137.37, 137.32, 128.98, 128.86, 128.72, 128.55, 128.47, 128.40, 128.31, 128.28, 128.19, 128.17, 128.16, 128.11, 128.06, 128.01, 127.93, 127.83, 127.80, 127.67, 127.62, 127.59, 127.56, 127.52, 127.47, 127.44, 127.41, 127.14, 127.04, 126.62, 126.58, 126.49, 126.42, 99.85, 99.83, 99.74, 99.71, 99.55, 99.39, 99.38, 99.27, 98.75, 80.96, 80.75, 80.66, 80.40, 80.18, 79.53, 79.07, 78.27, 75.90, 75.25, 74.99, 74.48, 74.21, 73.98, 73.43, 72.98, 72.71, 72.29, 71.82, 71.26, 70.69, 69.74, 69.68, 69.55, 69.23, 68.80, 66.50, 65.24, 62.23, 61.76, 34.57, 34.39, 32.20, 29.98, 29.95, 29.82, 29.76, 29.64, 29.56, 29.41, 29.38, 25.23, 25.15, 25.13, 22.99, 14.44; ^{31}P NMR($CDCl_3$, 121 MHz) δ 1.02, 0.93; MS for $C_{395}H_{459}O_{69}$ calcd 6337.2, found 6361.8 (M + Na).

Compound 1. Compound **46** (30 mg, 4.7 μmol) was dissolved in a mixture of MeOH/$CHCl_3$/H_2O (3:3:1, 3 mL). Pd/C (10%, 40 mg) was added. The mixture was stirred under H_2 (30 psi) for 3 h. The catalyst was filtered off, and the residue was purified through a column of Sephadex G-15 to give deprotected compound **1** (10 mg, 71%): ^{1}H NMR (d_6 DMSO, 300 MHz) δ 4.51−5.02 (m, 11 H), 2.61−4.23 (m, 78 H), 2.23−2.45 (m, 6H), 1.41 (m, 6H), 1.24 (m, 90 H), 0.89 (m, 6H); ^{31}P NMR(DMSO, 121 MHz) δ 0.61, 0.49; MS for $C_{129}H_{231}O_{69}$ calcd 2915.4, found 2961.6 (M + 2Na).

Acknowledgment. We are grateful to Dr. George Dubay, Director of Instrument Operations in the Department of Chemistry, Duke University, for the mass spectroscopy and MALDI measurements. We are grateful to the National Science Foundation (CHE 0243436 and 0717702) for support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802000P