Total synthesis of mycobacterial arabinogalactan containing 92 monosaccharide units

Yong Wu¹, De-Cai Xiong¹, Si-Cong Chen¹, Yong-Shi Wang¹ & Xin-Shan Ye¹

Carbohydrates are diverse bio-macromolecules with highly complex structures that are involved in numerous biological processes. Well-defined carbohydrates obtained by chemical synthesis are essential to the understanding of their functions. However, synthesis of carbohydrates is greatly hampered by its insufficient efficiency. So far, assembly of long carbohydrate chains remains one of the most challenging tasks for synthetic chemists. Here we describe a highly efficient assembly of a 92-mer polysaccharide by the preactivation-based one-pot glycosylation protocol. Several linear and branched oligosaccharide/polysaccharide fragments ranging from 5-mer to 31-mer in length have been rapidly constructed in one-pot manner, which enables the first total synthesis of a biologically important mycobacterial arabinogalactan through a highly convergent \([31 + 31 + 30]\) coupling reaction. Our results show that the preactivation-based one-pot glycosylation protocol may provide access to the construction of long and complicated carbohydrate chains.
Carbohydrates are involved in many key biological processes, such as cell signaling, cell proliferation and differentiation and viral and bacterial infections, as well as immunoresponse. Naturally occurring carbohydrates and glycoconjugates usually exist in microheterogeneous forms, making the isolation of pure carbohydrates and glycoconjugates from natural sources difficult or even impossible in most cases. Therefore, chemical synthesis becomes the main approach to obtain well-defined carbohydrates. However, unlike peptides and oligonucleotides, which can be routinely prepared by automated solid-phase synthesizers, the oligosaccharide synthesis is much more difficult. The major challenge for oligosaccharide preparation is the regio- and stereochemistry issues in each glycosidic bond formation, making oligosaccharide synthesis a tedious and time-consuming process. Therefore, oligosaccharide synthesis becomes a daunting task, especially when polysaccharides are chosen as the target molecules. Indeed, only a few examples of the synthesis of oligosaccharide sequences containing > 20 units have been reported over the past few decades. These syntheses are challenging because multiple steps of protective group manipulation and intermediate purification are required in most cases.

Arabinogalactan is an essential structural constituent of mycobacterial cell wall, which plays critical roles in the infectivity and pathogenicity of Mycobacterium tuberculosis. Based on experiments and analyses, the primary structure of arabinogalactan has been established as a linear galactan composed of about 30 alternating β-(1→5)-linked and β-(1→6)-linked α-galactofuranose (GalF) residues, to which up to two highly branched arabinan chains (each containing 31 D-arabino-

Oligosaccharides are the building blocks for polysaccharides. Therefore, the efficient synthesis of oligosaccharide fragments is crucial. Herein, we present our one-pot strategy for the rapid assembly of oligosaccharide fragments up to 31-mer. This strategy relies on the preactivation protocol to give a scalable one-pot coupling reaction to generate the linear and branched oligosaccharide fragments for the rapid assembly of polysaccharides up to 31-mer, and (4) the convergent 

Results

Retrosynthetic analysis. The target polysaccharide arabinogalactan 1 was disconnected into two sizeable fragments, that is, the linear GalF₃₀ acceptor 2 and the branched AraF₃₁ donor 3 (Fig. 1). It was conceived that GalF₃₀ acceptor 2 would be rapidly assembled via a five-component one-pot coupling of several oligosaccharide fragments 4–7. As for the synthesis of AraF₃₁, donor 3, oligosaccharide fragments 10–12 were designed to carry out a four-component one-pot glycosylation reaction. For the preparation of heptasaccharide 10, thioglycoside donors 13a–c and thioglycoside acceptor 14 were planned for the construction of the challenging β-arabinofuranosyl linkages. Finally, it was expected that all the oligosaccharide fragments (8, 9, 15–17) would be accessible by the preactivation-based one-pot oligosaccharide synthesis starting from various monosaccharide building blocks. Overall, it was anticipated that the major challenge of our plan towards the total synthesis of arabinogalactan 1 would rely on the efficiency of one-pot glycosylation reactions, especially when large oligosaccharide fragments were attempted as the components in one-pot coupling reactions.

Synthesis of GalF₃₀ acceptor 2. To test our one-pot strategy for oligosaccharide synthesis, three monosaccharide building blocks 18–20 were designed and synthesized (Supplementary Fig. 1). Using these building blocks, the assembly of hexasaccharide 8 in a six-component one-pot manner (18 + 19 + 20 + 19 + 20 + 19) by preactivation protocol was tried, which should be rather challenging as up to five glycosidic linkages must be correctly constructed. To our delight, when promoted by stoichiometric p-toluenesulfonyl chloride/silver trflate (p-TolSOCl/AgOTf), all glycosylation steps underwent smoothly and none of the side products interfered with the reaction. After optimization of the reaction conditions, hexasaccharide 8 was obtained in 63% overall yield and on a perfect scale (1.07 g) within several hours (Fig. 2a). The desilylation of 8 provided 5 (85% yield), which was re-protected with benzyl group to give 4 in 96% yield. Subsequently, the coupling reaction of 8 with 1-octanol afforded 21 (91% yield), which was followed by desilylation to provide 6 in 87% yield.

With hexasaccharides 4–6 in hand, the next, the further one-pot glycosylation was performed. The five-component one-pot coupling of these oligosaccharides (4 + 5 + 5 + 5 + 6) was realized successfully, producing the 30-mer polysaccharide 22 in 68% overall yield (Fig. 2b). It was noteworthy that some deletion sequences were difficult to be removed by column chromatography on silica gel. Gratifyingly, given the difference in molecular weight between the deletion sequences and desired product, size exclusion chromatography was then used to obtain the pure 30-mer polysaccharide 22 (Supplementary Fig. 2). The identity of 22 was confirmed by its nuclear magnetic resonance (NMR) and matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectra (see Supplementary Information for details). Finally, the global deprotection of 22 via successive debenzylation and debenzylation provided the 30-mer galactan 23 ([M+Na]+ m/z calc. for 5017.4, found: 5018.1).

Having established a highly efficient one-pot approach to the synthesis of polysaccharide up to 30-mer, we turned to accomplish the construction of GalF₃₀ acceptor 2. As shown in Fig. 1, an additional hexasaccharide 9 equipped with two levulinoyl groups was needed. Initially, monosaccharide 24a (Supplementary Fig. 3) was designed as a building block for a six-component one-pot assembly of 9. However, the efforts failed due to the migration of levulinoyl group from the O-5 to O-6 position. As an alternative route, disaccharide 24b was synthesized (Supplementary Fig. 3). Therefore, a four-component one-pot coupling reaction (18 + 24b + 24b + 19) finally gave the...
Figure 1 | The structure of mycobacterial arabinogalactan 1 and its retrosynthetic analysis. Bn, benzyl; Bz, benzoyl; Lev, levulinoyl; TBS, tert-butyl-dimethylsilyl; TIPDS, tetraisopropyldisiloxanylidene; TIPS, trisopropylsilyl; Tol, p-tolyl.
Synthesis of Ara\textsubscript{f1} donor 3. The assembly of the branched Ara\textsubscript{f1} donor 3 required three oligosaccharide intermediates, that is, \(\beta\)-Ara-containing heptasaccharide 10, branched pentasaccharide 11 and linear hexasaccharide 12. For this purpose, a set of arabinofuranosyl building blocks (13a–c, 26–29) were designed and synthesized (Supplementary Fig. 4). A six-component iterative one-pot glycosylation of monosaccharides 26 and 27 (26 + 27 + 27 + 27 + 27 + 27) afforded hexasaccharide 17 in excellent yield (73%) and on gram scale (1.20 g) (Fig. 3a). The desilylation of 17 resulted in the desired hexasaccharide 12 (92% yield). Likewise, the one-pot coupling reaction of building blocks 26, 28 (ref. 30) and 27 provided a branched pentasaccharide 16 very smoothly (78% yield), which was further converted into diol 11 by desilylation in 95% yield (Fig. 3b). For the preparation of heptasaccharide 10, another diol 14 was required. Initially, the glycosyl donor 29a (ref. 31) with chloroacetyl group at the O-2 position was chosen for the one-pot construction of pentasaccharide 15a (Supplementary Table 1), but the overall yield was moderate (43%). Fortunately, when the donor 29 equipped with a levulinoyl group was employed for the one-pot glycosylation reaction, pentasaccharide 15 was rapidly assembled in 76% overall yield (Fig. 3b). Ultimately, deacetylation of 15 gave diol 14 (94% yield).

Our attention was then turned to the synthesis of heptasaccharide 10, which involved the stereocontrolled installation of two challenging \(\beta\)-arabinofuranosyl linkages. Among a number of innovative glycosyl donors developed by several groups\textsuperscript{25–37}, perbenzyl-protected thioglycoside 13a (ref. 25) and 3,5-O-tetraisopropylidiloxanylidene-protected thioglycosides 13b,c (ref. 31) were synthesized for the current purpose (Supplementary Table 2). Although these donors proved useful for direct \(\beta\)-arabinofuranosylation, whether they could be subjected to thioglycoside acceptor 14 under the donor-preactivation conditions\textsuperscript{38} remained to be explored. After some optimization, the best result arose when 4.0 equiv. of 13b was preactivated by \(p\)-TolSCI/AgOTf and subsequently glycosylated with 1.0 equiv. of diol 14, delivering heptasaccharide 30b with good stereoselectivity (\(\beta,\beta\)-isomer/other isomers = 9/1). Removal of the silyl groups in 30b afforded 31 (74% over two steps, Fig. 3c), in which the newly formed \(\beta\)-arabinofuranosyl linkages were...
confirmed by the $^{13}$C NMR spectrum (appearance at 99.6 and 99.1 p.p.m.)\(^{35}\). Finally, the re-protection of 31 with benzoyl groups yielded the desired heptasaccharide 10 (97% yield).

With oligosaccharide building blocks 10–12 in hand, the assembly of Araf\(_3\) donor 3 by preactivation-based one-pot glycosylation protocol was attempted. This one-pot reaction was expected to be more challenging due to the steric hindrance in the double glycosylation of Araf\(_3\) acceptor 11 using Araf\(_2\) donor 10. Surprisingly, the reaction proceeded smoothly when 2.3 equiv. of 10 was reacted with 1.0 equiv. of 11, delivering an Araf\(_{3,9}\) intermediate, which was sequentially coupled with two Araf\(_6\) acceptors 12 in a single flask without any intermediate isolation to afford the Araf\(_{3,9}\) donor 3 in 70% overall yield (Fig. 3d). To further confirm the identity of this 31-mer polysaccharide, an Araf\(_6\) acceptor 32 bearing an alkyl group at the reducing end was synthesized (Fig. 3a). Thus a four-component one-pot coupling reaction of oligosaccharides 10–12 and 32 gave a similar 31-mer polysaccharide 33 in 65% yield (Fig. 3d), which was fully deprotected via deacetylation and hydrogenolysis to afford the arabinan 34 ([M + Na]\(^{+}\) monoisotopic m/z calcd. for 4246.4, found: 4246.3; [M + K]\(^{+}\) monoisotopic m/z calcd. for 4262.4, found: 4262.2). Gratifyingly, the $^1$H and $^{13}$C NMR data of 34 were found to be identical with previous reports\(^{14,40}\) except for the differences in some repeating units.

Assembly of arabinogalactan 1. Our final task was the glycosylation of Galf\(_{30}\) acceptor 2 with Araf\(_3\) donor 3 to finish the assembly of target polysaccharide. To the best of our knowledge, no glycosylation reactions between polysaccharide sequences composed of > 20 units were reported to date. For the planned 31 + 31 + 30 coupling reaction, it was anticipated that the biggest challenge would come from the steric hindrance by the bulky size of both the donor and acceptor, especially when a double glycosylation was required. Indeed, when a wide variety of promoter systems such as p-TolSCI/AgOTf\(^{29}\), NIS/AgOTf\(^{41}\), NIS/TfOH\(^{42}\), N-(p-methylphenylthio)-\(\varepsilon\)-caprolactam/Tf\(_2\)O\(^{43}\), TBPA\(^{44}\), Ph3Bi(OTf)\(_2\) (ref. 45), BSP/Tf\(_2\)O\(^{46}\) and Ph2SO/Tf\(_2\)O\(^{47}\) were examined (Supplementary Table 3), no double glycosylation product or only some monoglycosylation product was observed before the donor decomposed, prompting us to further screen the reaction conditions. Encouragingly, it was found that benzenesulfinyl morpholine/triflic anhydride (BSM/ Tf\(_2\)O)\(^{48}\) developed by our group is the most effective promoter. And indeed, when promoted by BSM/Tf\(_2\)O, this double
glycosylation was extremely clean and complete (indicated by thin-layer chromatography analysis), delivering the fully protected arabinogalactan 35 in 84% yield (Fig. 4). Although signals of the anomeric protons in 1H NMR spectrum were obscured due to the extensive overlapping, the anomeric carbons were distinctive in 13C NMR spectrum (all anomeric carbons of x-Araf residues and β-Galf residues were between 105 and 107 p.p.m., and anomic carbons of β-Araf residues appeared at 101.0 and 100.6 p.p.m.). The identity of 35 was further supported by its MALDI-TOF mass spectrum ([M+Na]⁺ m/z calcd. for 33885.4, found: 33884.7). Finally, the global deprotection of 35 by the successive deacylation and hydrogenolysis was conducted, affording the target polysaccharide arabinogalactan 1 successfully.

**Discussion**

We have developed a concise and highly efficient strategy for the first total synthesis of 92-mer mycobacterial arabinogalactan 1. This work not only represents the longest well-defined carbohydrate chain up to date, but also provides useful compounds as probes for further investigations on mycobacterial cell wall-related biological events. Our synthetic strategy highlights a series of efficient preactivation-based one-pot glycosylation reactions to minimize the synthetic steps, the stereoselective β-arabinofuranosylation by preactivation protocol and the convergent [31 + 31 + 30] double glycosylation reaction, thus offering a straightforward access to the target polysaccharide. Our work may open an avenue to the synthesis of complex polysaccharides with biological importance that are either difficult or impossible to access through isolation or semisynthesis.

**Methods**

**General**. The complete experimental details and compound characterization data can be found in Supplementary Methods. For the NMR, HPLC and MALDI-TOF mass spectra of the compounds in this article, see Supplementary Figs 5–126.

**General procedure for preactivation-based one-pot glycosylation reaction.** A mixture of glycosyl donor, TTBp and freshly activated 4 Å molecular sieves in anhydrous CH2Cl2 under argon atmosphere was stirred for 20 min at room temperature and cooled to −78 °C. After 5 min, stoichiometric amount of p-TolSCI was added to the mixture, followed by the addition of AgOTf. After another 5 min, a solution of glycosyl acceptor in anhydrous CH2Cl2 was slowly added. The resulting mixture was slowly warmed to room temperature within 2 h, stirred for another 20 min and cooled back to −78 °C. The glycosylation operation mentioned above was repeated until the generation of the desired product.

**Data availability.** The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information files. And all data are available from the authors upon reasonable request.

**References**

1. Varki, A. Biological roles of oligosaccharides: all of the theories are correct. Glycobiology 3, 97–130 (1993).
2. Bertozzi, C. R. & Kiessling, L. Chemical glycochemistry. Science 291, 2357–2364 (2001).
3. Bolte, T. J., Buskas, T. & Boons, G.-J. Opportunities and challenges in synthetic oligosaccharide and glycoconjugate research. Nat. Chem. 1, 611–622 (2009).
4. Danishefsky, S. J., McClure, K. F., Randolph, J. T. & Ruggeri, R. B. A strategy for the solid-phase synthesis of oligosaccharides. Science 260, 1307–1309 (1993).
5. Yamada, H., Harada, T., Miyazaki, H. & Takahashi, T. One-pot sequential glycosylation: a new method for the synthesis of oligosaccharides. Tetrahedron Lett. 35, 3979–3982 (1994).
6. Zhang, Z. et al. Programmable one-pot oligosaccharide synthesis. J. Am. Chem. Soc. 121, 734–753 (1999).
7. Plante, O. J., Palmacci, E. R. & Seeberger, P. H. Automated solid-phase synthesis of oligosaccharides. Science 291, 1523–1527 (2001).
8. Nigulker, S. S. & Demchenko, A. V. Stereoregulated 1,2-cis glycosylation as the driving force of progress in synthetic carbohydrate chemistry. Chem. Sci. 6, 2687–2704 (2015).
9. Wang, C.-C. et al. Regioselective one-pot protection of carbohydrates. Nature 446, 896–899 (2007).
10. Matsuoka, Y., Ito, Y., Nakahara, Y. & Ogawa, T. Synthesis of branched poly-N-acetyl-lactosamine type pentaantennary pentacosasaccharide: glyc an part of a glycosyl ceramide from rabbit erythrocyte membrane. Tetrahedron Lett. 34, 1061–1064 (1993).
11. Pozsgay, V. A new strategy in oligosaccharide synthesis using lipophilic protecting groups: synthesis of a tetracosasaccharide. Tetrahedron: Asymmetry 11, 151–172 (2000).
12. Fraser-Reid, B., Lu, J., Jayaprakash, K. N. & Lopez, J. C. Synthesis of a 28-mer oligosaccharide core of Mycobacterial lipoarabinomannan (LAM) requires only two n-pentenyl orthoester progenitors. Tetrahedron: Asymmetry 17, 2449–2463 (2006).

**Figure 4 | Assembly of arabinogalactan 1.** Reagents and conditions: (1) BSM, Tf2O, 4 Å MS, CH2Cl2, −40 °C; (2) NaOCH3, CH3OH/THF (2:1); (3) Pd/C, H2, EtOAc/THF/1-PrOH/H2O (2:1:1:1). BSM, benzenesulfinyl morpholine.
13. Mereyala, H. B., Hotha, S. & Gurjar, M. K. Synthesis of pentaarabinofuranosyl
14. Joe, M., Bai, Y., Nacario, R. C. & Lowary, T. L. Synthesis of the
docosasaccharide arabinan motif of
15. Ishiwata, A. & Ito, Y. Synthesis of docosasaccharide arabinan domain of mycobacterial arabinogalactan.
16. Calin, O., Eller, S. & Seeberger, P. H. Automated polysaccharide
17. Cheon, H.-S., Lian, Y. & Kishi, Y. Highly stereoselective and iterative synthesis of highly branched
18. Completo, G. C. & Lowary, T. L. Synthesis of galactofuranose-containing
19. D’Souza, F. W. & Lowary, T. L. The first total synthesis of a highly branched
20. Alderwick, L. J. et al. Deletion of Cg-emb in corynebacteriae results to a novel
truncated cell wall arabinogalactan, whereas inactivation of Cg-ubiA results in an arabinan-deficient mutant with a cell wall galactan core. J. Biol. Chem. 280, 32362–32371 (2005).
21. Hamidi, S. et al. The identification and location of succinyl residues and the characterization of the interior arabinan region allow for a model of the complete primary structure of Mycobacterium tuberculosis mycolyl arabinogalactan. J. Biol. Chem. 283, 12992–13000 (2008).
22. Bhamidi, S. et al. Detailed structural and quantitative analysis reveals the spatial organization of the cell wall of in Vivo grown Mycobacterium leprae and in vitro grown Mycobacterium tuberculosis. J. Biol. Chem. 286, 23168–23177 (2011).
23. Lowary, T. L. Twenty years of mycobacterial glycas: furanosides and beyond. Acc. Chem. Res. 49, 1379–1388 (2016).
24. Mereyala, H. B., Hotha, S. & Gauraj, M. K. Synthesis of pentaarabinofuranosyl structure motif A of Mycobacterium tuberculosis. J. Chem. Soc. Commun. 685–686 (1998).
25. D’Souza, F. W. & Lowary, T. L. The first total synthesis of a highly branched arabinofuranosyl hexaxaraccharide found at the nonreducing termini of mycobacterial arabinogalactan and lipoarabinomannan. Org. Lett. 2, 1493–1495 (2000).
26. Completo, G. C. & Lowary, T. L. Synthesis of galactofuranose-containing acceptor substrates for mycobacterial galactofuranosyltransferases. J. Org. Chem. 73, 4513–4525 (2008).
27. Wang, S., Meng, X., Huang, W. & Yang, J.-S. Influence of silyl protections on the anomic reactivity of galactofuranosyl thioglycosides and application of the silylated thiolgalactofuranosides to one-pot synthesis of diverse β-D-galactofuranosides. J. Org. Chem. 79, 10203–10217 (2014).
28. Kandasamy, J., Hurevich, M. & Seeberger, P. H. Automated solid phase synthesis of oligoarabinofuranosides. Chem. Commun. 49, 4453–4455 (2013).
29. Huang, X., Huang, L., Wang, H. & Ye, X.-S. Iterative one-pot synthesis of oligosaccharides. Angew. Chem. Int. Ed. 43, 5221–5224 (2004).
30. Li, R.-Y., Deng, L.-M., Liu, X. & Yang, J.-S. Efficient one-pot syntheses of β-D-arabinofuranosyl tri- and tetrascaracharides present in cell wall polysaccharide of Mycobacterium tuberculosis. Tetrahedron 66, 87–93 (2010).
31. Ishiwata, A., Akao, H. & Ito, Y. Stereoselective synthesis of a fragment of mycobacterial arabinan. Org. Lett. 8, 5525–5528 (2006).
32. Gaidotat, R. R., Callam, C. S., Wagner, T., Fraino, B. D. & Lowary, T. L. 2,3-Anhydro sugars in glycolide bond synthesis. Highly stereoselective syntheses of oligosaccharides containing α- and β-arabinofuranosyl linkages. J. Am. Chem. Soc. 125, 4155–4165 (2003).
33. Lee, Y. J., Lee, K., Jung, E. H., Jeon, H. B. & Kim, K. S. Acceptor-dependent stereoselective glycosylation: 2-CB glycoside-mediated direct β-D-arabinofuranosylation and efficient synthesis of the octaarabinofuranoside in mycobacterial cell wall. Org. Lett. 7, 3263–3266 (2005).
34. Zhu, X., Kawatkar, S., Rao, Y. & Boons, G.-J. Practical approach for the stereoselective introduction of β-arabinofuranosides. J. Am. Chem. Soc. 128, 11948–11957 (2006).
35. Inamurara, A. & Lowary, T. L. β-Selective arabinofuranosylation using a 2,3-O-(2-quinoledinylcarbonyl) substituted ethyl thioglycoside donors. Org. Lett. 15, 3974–3977 (2013).
36. Crich, D., Pedersen, C. M., Bowers, A. A. & Wink, D. J. On the use of 3,5-O-benzylidene and 3,5-O-(di-tert-butylidene)-2-O-benzylarabinofuranosides and their sulfonates as glycosyl donors for the synthesis of β-arabinofuranosides: importance of the activation method. J. Org. Chem. 72, 1553–1565 (2007).
37. Mizutani, K., Kasai, R., Nakamura, M. & Tanaka, O. N.M.R. spectral study of α- and β-L-arabinofuranosides. Carbohydr. Res. 185, 27–38 (1989).
38. Lee, R. E. B., Li, W., Chatterjee, D. & Lee, R. E. Rapid structure characterization of the arabinogalactan and lipoarabinomannan in live mycobacterial cells using 2D and 3D HMR-MS-MS: structural changes in the arabinan due to ethambutol treatment and gene mutation are observed. Glycobiology 15, 139–151 (2005).
39. Konradsson, P., Udomong, U. E. & Fraser-Reid, B. Liodonium promoted reactions of disarmed thioglycosides. Tetrahedron Lett. 31, 4313–4316 (1990).
40. Vwnman, G. H., van Leeuwen, S. H. & van Boom, J. H. Liodonium ion promoted reactions at the anomic centre. II. An efficient thioglycoside mediated approach toward the formation of 1,2-trans linked glycosides and glycosidic esters. Tetrahedron Lett. 31, 1331–1334 (1990).
41. Maitiy, S. K., Basu, N. & Ghosh, R. Efficient activation of thioglycosides with N-(p-methylene phenylthio)-e-caprolactam-TMSOTf. Carbohydr. Res. 354, 40–48 (2012).
42. Marra, A., Mallet, J.-M., Amatore, C. & Siray, P. Glycosylation using a one-electron-transfer homogeneous reagent: a novel and efficient synthesis of β-linked disaccharides. Synlett 572–574 (1990).
43. Gossawi, M., Ellern, A. & Pohl, N. L. Bismuth(V)-mediated thioglycoside activation. Angew. Chem. Int. Ed. 52, 8441–8445 (2013).
44. Crich, D. & Smith, M. 1-Benzensulfinyl piperidine/trifluoromethanesulfonic anhydride: a potent combination of shelf-stable reagents for the low-temperature conversion of thioglycosides to glycosyl triflates and for the formation of diverse glycosidic linkages. J. Am. Chem. Soc. 123, 9015–9020 (2001).
45. Codée, J. H. D. C. et al. Ph3SO/TF2O: A powerful promoter system in chemoselective glycosylations using thioglycosides. Org. Lett. 5, 1519–1522 (2003).
46. Wang, C., Wang, H., Huang, X., Zhang, L.-H. & Ye, X.-S. Benzensulfinyl morpholine: a new promoter for one-pot oligosaccharide synthesis using thioglycosides by pre-activation strategy. Synlett 2846–2850 (2006).

Acknowledgements
This work was financially supported by the grants from the National Natural Science Foundation of China (21232002) and the Ministry of Science and Technology of China (2013CB910700, 2012CB822100). We thank Professor Qin Li and Professor Lijun Zhong at Peking University Health Science Center for their helpful assistance in analysis of glycans structures.

Author contributions
D.-C.X. and X.-S.Y. conceived the research. Y.W., D.-C.X. and X.-S.Y. designed the experiments. Y.W. performed all the experiments. S.-C.C. and Y.-S.W. synthesized some building blocks. Y.W., D.-C.X. and X.-S.Y. analyzed the data. Y.W. and X.-S.Y. wrote the manuscript. X.-S.Y. supervised the project.

Additional information
Supplementary Information accompanies this paper at http://www.nature.com/naturecommunications

Competing interests: The authors declare no competing financial interests.

Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/

How to cite this article: Wu, Y. et al. Total synthesis of mycobacterial arabinogalactan containing 92 monosaccharide units. Nat. Commun. 8, 14851 doi:10.1038/ncomms14851 (2017).

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

© The Author(s) 2017