A New Strategy for Oligosaccharide Assembly Exploiting Cyclohexane-1,2-diacetal Methodology: An Efficient Synthesis of a High Mannose Type Nonasaccharide

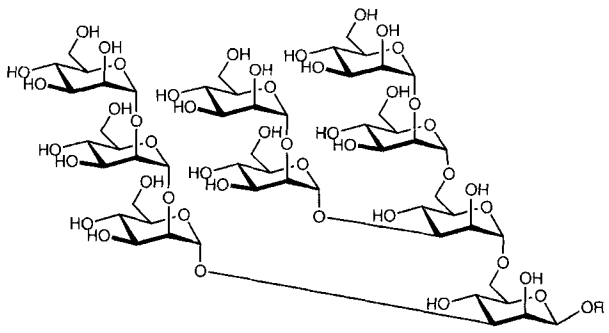
Peter Grice, Steven V. Ley,* Jörg Pietruszka, Helen M. I. Osborn, Henning W. M. Priepke, and Stuart L. Warriner

Abstract: The high-mannose nonasaccharide **1** is part of the glycoprotein gp120 of the viral coat of HIV-1. The mannan portion of this triantennary glycan was prepared by a number of consecutive glycosidation steps without the need for any protecting-group manipulation. This was achieved by carefully tuning the reactivity of the glycosyl donors by employing our cyclohexane-1,2-diacetal (CDA) methodology. The method was further extended with *one-pot* procedures for oligosaccharide synthesis, thus reducing the number of steps to form the protected nonasaccharide **21** from the monosaccharide building blocks to five.

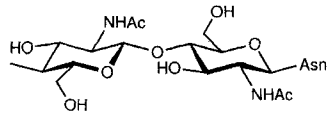
Keywords
carbohydrates · glycoproteins · HIV · oligosaccharides · protecting groups

Introduction

Carbohydrates continue to be a focus of research both in chemistry and biology. Spectacular advances in analytical methods have confirmed that carbohydrates are not only widespread, renewable stores of energy and skeletal components,[1] but that they also play a critical role in a variety of biochemical processes.[2] The structural diversity of sugar oligomers leads to their involvement in many key inter- and intracellular events.[3] In particular, the glycans of glycoconjugates are vital for biological recognition processes. Cell-surface carbohydrates serve as points of attachment for cells, bacteria, viruses, toxins and a plethora of other molecules.[4] As a consequence, carbohydrates are intrinsically involved in the genesis of numerous diseases; for instance, it is well established that tumour cells display an aberrant glycosylation in their cell membranes.[5] These and other important discoveries have stimulated intense research interest in oligosaccharides, focusing on both their synthesis and function.



1 R =



2 R = $-(CH_2)_8CO_2Me$

High mannose type oligosaccharides such as **1** are ubiquitous in nature.[6] They are a member of the *N*-linked family of carbohydrates which are conjugated to glycoproteins via an *N*-acetylglucosamine unit to the amide group of an asparagine (Asn) residue on the polypeptide backbone. In particular Mizuochi et al. have shown that 29 different *N*-linked oligosaccharides are present on the envelope glycoprotein gp120 of the human immunodeficiency virus (HIV), which is known to bind with high affinity to human T4 lymphocytes causing AIDS (acquired immunodeficiency syndrome).[7] The chemical synthesis of segments of this binding region is of interest not only for the determination of their structure and/or conformation, but also to provide a supply of biological probes: oligosaccharides bound via a spacer to larger molecules act as suitable antigens for the production of monoclonal antibodies or may be used as material for affinity chromatography of enzymes and antibodies. Since gp120 has been implicated in the attachment and penetration of target cells and in the antiviral immune re-

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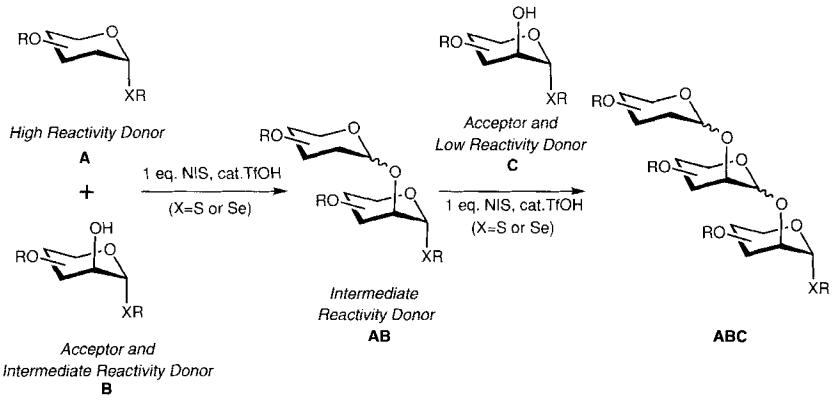
sponse,[8] it has also been anticipated that the glycans of the viral envelope are also possible targets for immunotherapy as well as vaccine development.[9] Müller et al.[10] have demonstrated the in vitro activity of antibodies directed against the mannose residues of HIV-1 glycoprotein gp120, and this result makes this mannan moiety an especially attractive synthetic target.[11]

We recently introduced the new CDA (cyclohexane-1,2-diacetal) protecting group for vicinal, diequatorial diol units.[12] This group was found not only to conveniently protect the 3,4-diol unit of mannosides in one step,[12a, e] but also proved to be a powerful tool for tuning the reactivity of glycosyl donors.[12b, c, d] This has allowed the assembly of versatile oligosaccharide building blocks without the need for any protecting group manipulations. Furthermore, our strategy enabled the highly efficient, one-pot synthesis of these fragments.[13, 12b, c] We have demonstrated that four different levels of reactivity can be attained, using only one promotor system (*N*-iodosuccinimide/triflic acid, NIS/TfOH).[14] In this paper we describe the synthesis of nonasaccharide **2**. Earlier studies have indicated that the two *N*-acetylglucosamine residues of **1** are not essential for specific binding of the mannan moiety to target systems and may be replaced with the 8-(methoxycarbonyl)octyl group. This group also presents the opportunity for linking of the glycan to a protein or solid support to give a number of desirable biological tools.[15]



Scheme 1. General approach to the chemoselective synthesis of a trisaccharide by careful tuning of glycosyl donor reactivity.

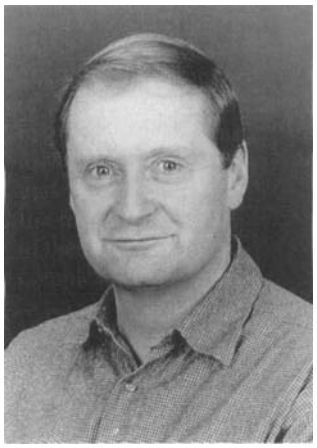
Results and Discussion

Classical strategies for oligosaccharide assembly are typically extended in character. In such schemes glycosidic bond forming steps are separated by unmasking procedures which reveal the donor or acceptor functionality required for the next coupling reaction. Such protecting group manipulations increase the linearity and decrease the efficiency of glycoside construction. Our strategy greatly condenses the process of oligosaccharide assembly by removing the need for unmasking steps between coupling protocols. The need for such reactions is obviated by the use of designed, chemoselective, glycosidation sequences.

The synthetic plan was based upon the ability to control the reactivity of thioethyl and selenophenyl glycosyl donors by careful choice of anomeric substituent and hydroxyl protecting groups. Selenoglycosides are more reactive than their sulfur analogues and the hydroxyl protecting groups have been shown to have profound influences on glycosyl donor reactivity.[16] As iodonium transfer to the sulfur or selenium atoms is rapid and reversible under the conditions of the reaction only the most reactive glycosyl donor in the mixture is activated when one equivalent of NIS is used. Sequential addition of equivalents of NIS and acceptor units thus allows the rapid, controlled synthesis of complex carbohydrate structures.

The concept is illustrated in Scheme 1 by the synthesis of general trisaccharide **ABC**. The synthesis is designed such that the protecting groups and the anomeric substituent of the building blocks give a decrease in reactivity of the donor functionality from the nonreducing to the reducing end of the trisaccharide. The key to the strategy is fragment **B**, which contains both donor and acceptor functionality. In the first reaction **A** and **B** are mixed and one equivalent of NIS added. In this process **B** is the less reactive glycosyl donor, and hence **A** is activated and trapped with the free hydroxyl of **B** giving the disaccharide **AB**. In the second reaction **AB** is mixed with **C** and a further equivalent of NIS added. In this case the donor functionality of **B** is the more reactive and so the disaccharide is activated and trapped with the hydroxyl of **C** to give the trisaccharide. The efficiency of the process can be further improved by performing the reactions in "one pot" without isolation of the intermediate disaccharide.

The strategy for the synthesis of **2** is outlined in Scheme 2. Four levels of reactivity should be sufficient to assemble the



Editorial Board Member:[*] *Steven Ley obtained his PhD from Loughborough University studying with Harry Heaney before carrying out post-doctoral work at Ohio State University with Leo Paquette and at Imperial College with Sir Derek Barton. Since 1992 he has held the position of BP (1702) Professor of Organic Chemistry at the University of Cambridge and a Ciba Research Fellowship. His research involves the discovery and development of new synthetic methods and their application to the synthesis of biologically important molecules. His group have published on a wide variety of subjects, ranging from the chemistry of iron carbonyl complexes to the design of novel reagents for oxidative transformations. Currently Professor Ley is investigating the synthesis of several important natural products, including azadirachtin, okadaic acid, rapamycin and spongistatin. In addition, his group is also developing new methods and strategies for efficient oligosaccharide assembly, research which is illustrated in the accompanying paper.*

[*] Members of the Editorial Board will be introduced to the readers with their first manuscript.

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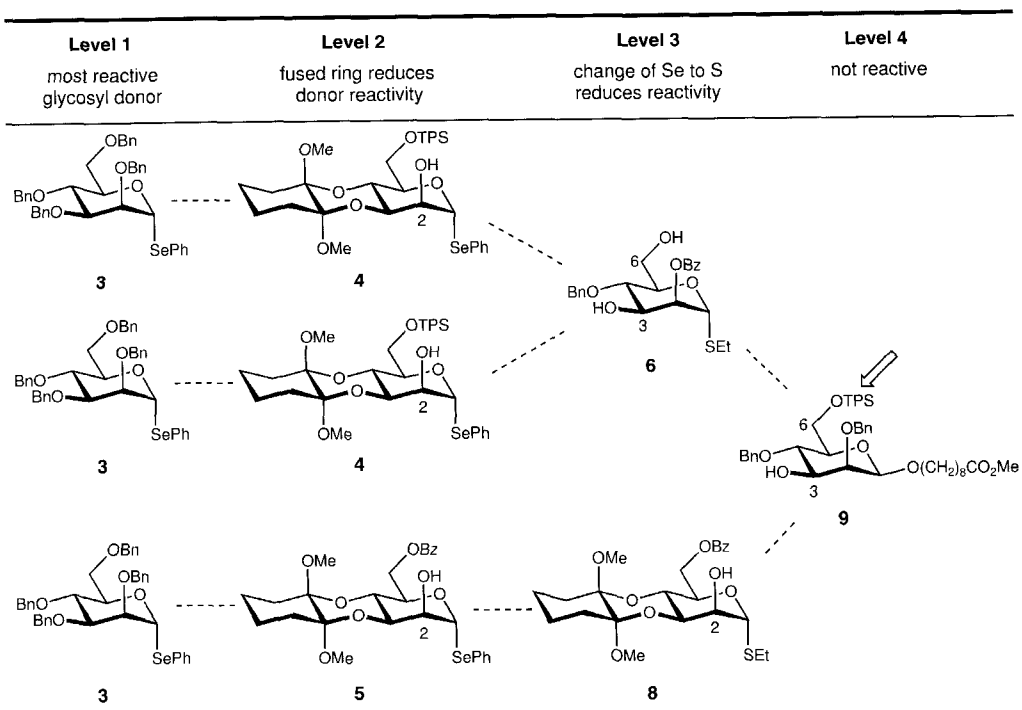
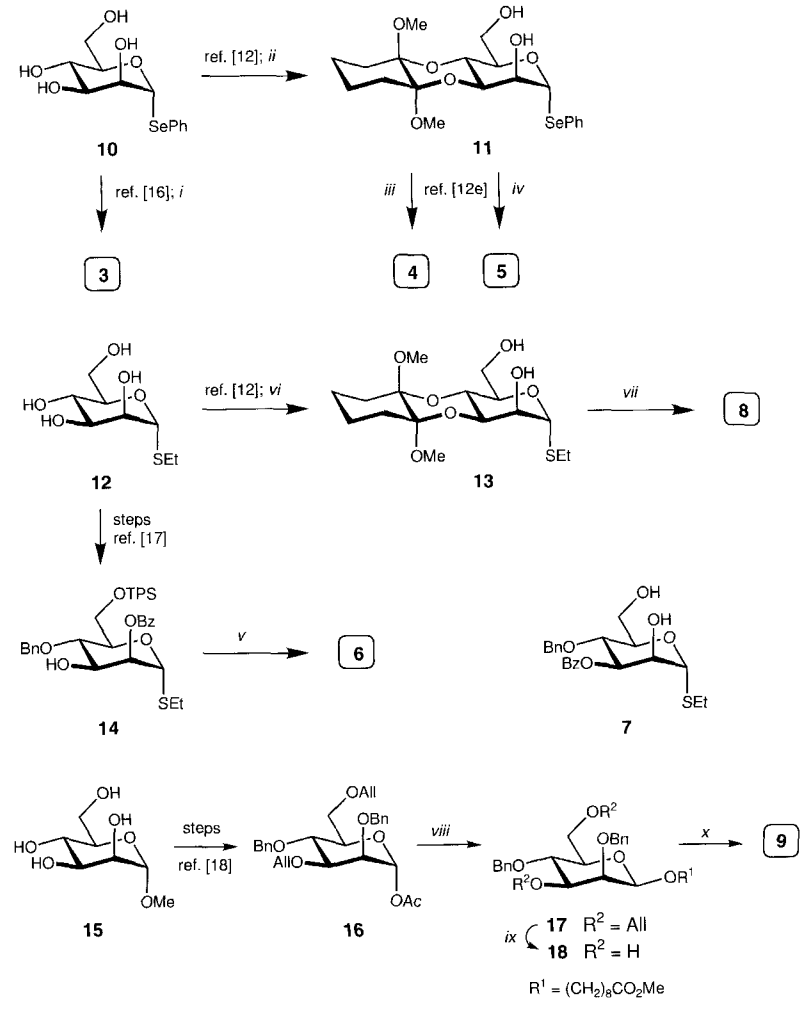


Scheme 2. Strategy for the assembly of the target nonasaccharide: the relative reactivities of glycosyl donors towards the promotor system NIS/TfOH are given. The arrow indicates the only essential protecting group manipulation.

nonasaccharide framework of **2** without the need for repeated protecting-group manipulations common to other routes. In fact, it was envisaged that for this highly convergent synthesis, only one deprotection step would be necessary during the assembly of the oligosaccharide (the *tert*-butyldiphenylsilyl (TPS) group of **9**). The most reactive glycosyl donor with respect to the promotor system NIS/TfOH is the per-*O*-benzylated phenylseleno donor **3**, and hence this provides the level 1 activity. The reactivity of bifunctional selenoglycosides **4** and **5** is reduced by the presence of the fused rings of the CDA protecting groups. These units provide the second level in the strategy. The third reactivity level is obtained by changing the anomeric leaving group from SePh to SEt in **6** and **8**. With these building blocks it is not only feasible to synthesise the required trisaccharide from **3**, **5** and **8**, but also the pentasaccharide from **3**, **4** and **6**. The former could in turn couple with the acceptor **9** (unreactive towards NIS/TfOH) to yield a tetrasaccharide, which could then be coupled with the pentasaccharide in the final glycosidation step.

The building blocks **3**–**9** were readily prepared by standard techniques (Scheme 3). The more reactive level 1 and level 2 donors were prepared from phenyl-1-seleno-α-D-mannopyranoside **10**. Per-*O*-benzylation gave the highly reactive donor **3** (78%),[17] which is the unit that provides all three, nonreducing termini in the synthesis. Using our CDA-methodology,[12] we could selectively protect the *trans*-1,2-diol unit of **10** in one step to give **11**. Selective silylation and benzoylation[12c–e] then gave the bifunctional units **4** (95%) and **5** (81%), respectively, in a very concise manner. The lower

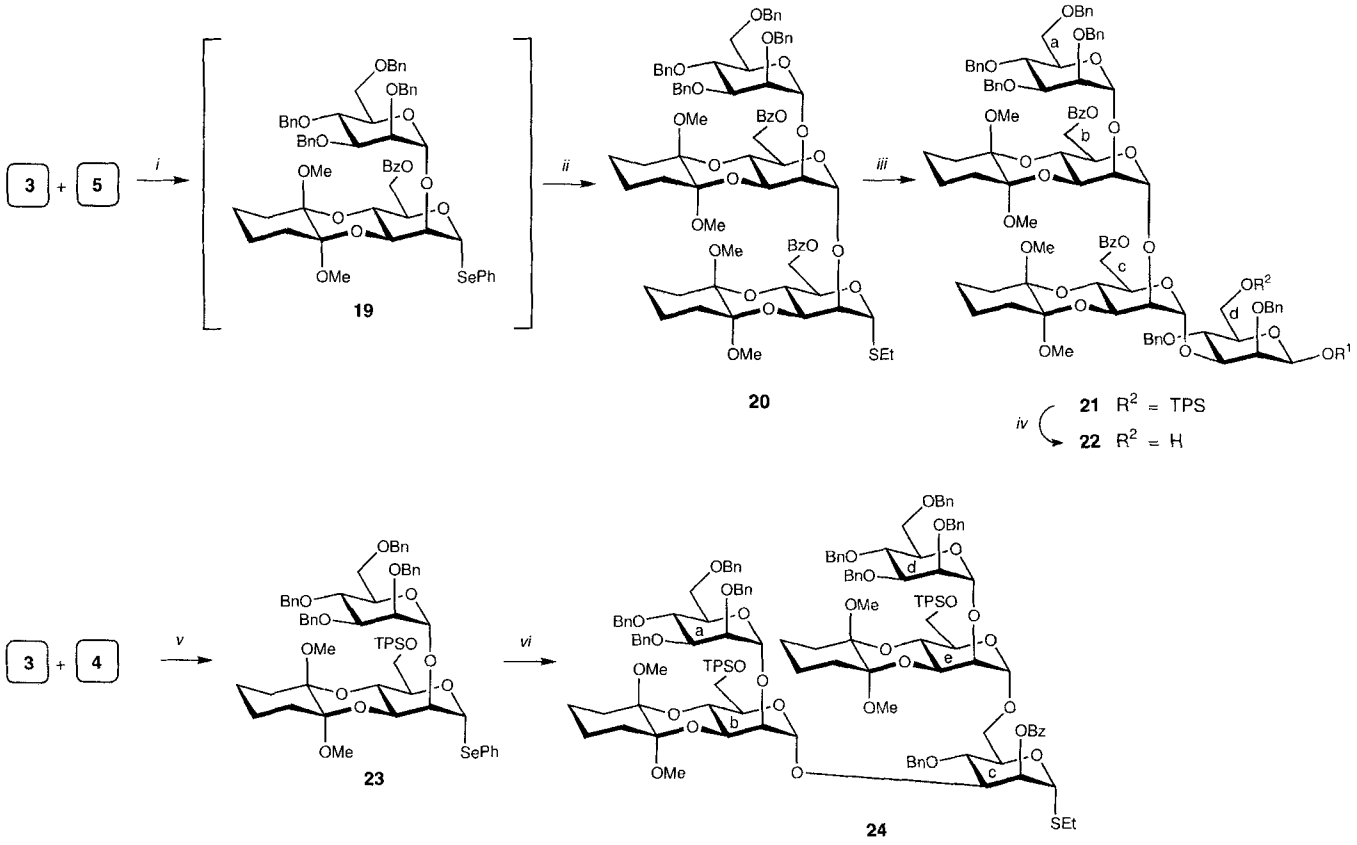


Scheme 3. *i*) NaH, BnBr, DMF, 78%. *ii*) 1,1,2,2-tetramethoxycyclohexane, MeOH, camphorsulfonic acid, $CH(OMe)_3$, reflux, 44%. *iii*) TPS-Cl, imidazole, THF, 95%. *iv*) $(Bu_3Sn)_2O$, reflux, toluene; 0 °C, BzCl, 76%. *v*) TBAF, cat. AcOH, THF, 68%. *vi*) 1,1,2,2-tetramethoxycyclohexane, MeOH, camphorsulfonic acid, $CH(OMe)_3$, reflux, 53%. *vii*) $(Bu_3Sn)_2O$, reflux, toluene; 0 °C, BzCl, 81%. *viii*) $TiBr_4$, dichloromethane, 3 h; Ag-silicate, 4 Å molecular sieves, $HO(CH_2)_8CO_2Me$, 3 d, −40 to 0 °C, 79%. *ix*) Pd/C, TsOH, MeOH, 86%. *x*) TPS-Cl, imidazole, THF, 88%. Bn = benzyl, Bz = benzoyl, Ac = acetyl, TPS = *tert*-butyldiphenylsilyl, All = allyl.

reactivity donors were prepared from ethyl-1-thio-mannopyranoside **12**. CDA protection again provided the 2,6-diol **13** in one step. Selective benzoylation of the 6-hydroxyl gave the required unit **8**.[12c–e] The known mannose derivative **14** could also be obtained from **12**.[18] Desilylation of **14** using fresh tetrabutylammonium fluoride (TBAF) buffered with acetic acid afforded the branch point **6** (68%). The use of unbuffered or old TBAF solution led to the migration of the benzoyl group into the thermodynamically more favourable 3-position of the mannoside, thus giving **7** instead of **6**. The remaining fragment, the β-mannoside **9**, was prepared from the known compound **16**[19] by the method established by Paulsen et al.[20] to introduce the difficult β-linkage. Titanium tetrabromide converted **16** into the anomeric bromide, which, in the presence of 8-(methoxycarbonyl)-octan-1-ol and heterogenous silver silicate promotor,[20a] produced almost exclusively the β-glycoside **17** (79%, $\beta:\alpha > 13:1$). The α-anomer was easily removed by flash column chromatography. Thorough temperature control and appropriate choice of protecting groups was absolutely essential for a high yield and good β-selectivity, as even remote protecting groups can affect the $\beta:\alpha$ ratio.[21] Deallylation of **17** was performed with Pd/C and *p*-toluenesulfonic acid in methanol to furnish the reported compound **18** (86%).[22] Finally, silylation of the 6-hydroxyl group afforded **9** in a good yield (88%).

With these building blocks in hand it was possible to begin the assembly of the target oligosaccharide (Scheme 4). Coupling of **3** with **5** with 1.2 equiv of NIS and catalytic amounts of TfOH was highly selective as our CDA protecting group reduces the reactivity of **5** as a glycosyl donor. The formation of disaccharide **19** was extremely satisfactory, and hence its isolation was not required. Simple addition of the third component **8** and a further 1.6 equiv of NIS produced the trisaccharide **20**, in one pot, in an excellent 67% yield. We were unable to activate the 1-thioglycoside **20** with NIS/TfOH, however, activation with bromine and silver triflate (AgOTf) in the presence of **9** realised the convenient synthesis of the tetrasaccharide **21** (60%).[23] According to Kihlberg this transformation proceeds via in situ formation of the anomeric bromide; however, other activation methods can also be envisaged. Desilylation of **21** afforded the acceptor **22** ready for the final coupling (87%).

Synthesis of the pentasaccharide required more subtle controls on the reactivity of the donors and illustrated the need to consider even remote protecting groups in the design of selective glycosylation sequences. Attempts to couple disaccharide **19** with **6** failed to yield the desired pentasaccharide, as **19** was not sufficiently reactive to give selectivity in the coupling. Clearly a more reactive disaccharide donor was required for the synthesis of this unit. Use of the alternative silyl-protected monosaccharide building block **4**, however, allowed the pentasaccharide to be synthesised with ease. The coupling of blocks **4** and **3** selectively produced the disaccharide **23**, although the moderate yield (46%, up to 55% on a small scale) and the formation of some trisaccharide by-products indicated that the tuning of the reactivity of the two systems was on the limit for selective reaction. Two equivalents of **23**, however, reacted with diol **6**, yielding the pentasaccharide **24** in an excellent 63% yield, ready for



Scheme 4. *i*) NIS, cat. TfOH, 4 Å molecular sieves, dichloroethane:ether 1:1, 10 min, then: *ii*) **8**, NIS, cat. TfOH, 4 Å molecular sieves, dichloroethane:ether 1:1, 1 h, 67%. *iii*) **9**, 4 Å molecular sieves, dichloromethane, 2,6-di-*tert*-butylpyridine, AgOTf; bromine, 3 d, 60%. *iv*) TBAF, cat. AcOH, THF, 87%. *v*) NIS, cat. TfOH, 4 Å molecular sieves, dichloroethane:ether 1:1, 5 min, 46%. *vi*) **6**, NIS, cat. TfOH, 4 Å molecular sieves, dichloroethane:ether 1:1, 5 min, 63%. $R^1 = (CH_2)_8CO_2Me$.

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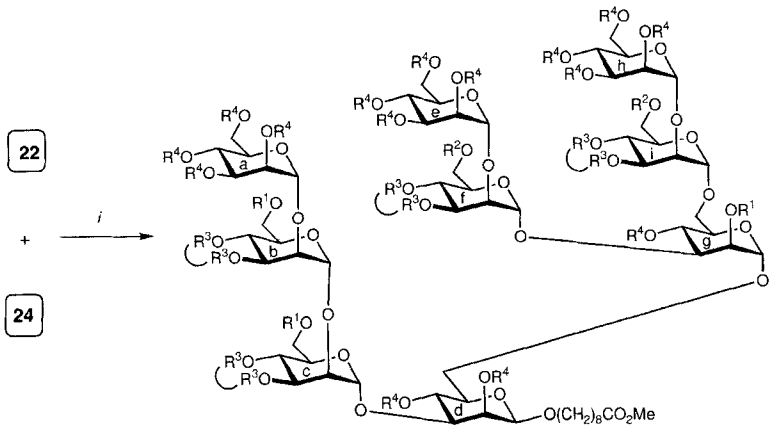
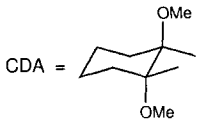
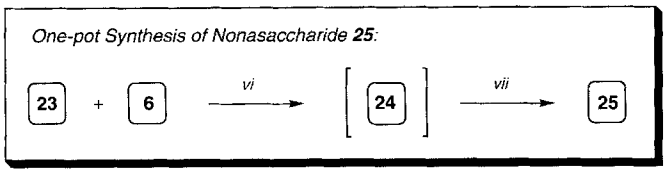


	R^1	R^2	R^3 R^3	R^4
25	Bz	TPS	CDA	Bn
26	H	TPS	CDA	Bn
27	H	H	CDA	Bn
28	H	H	H, H	Bn
2	H	H	H, H	H



ii iii iv v



Scheme 5. *i*) NIS, cat. TfOH, 4 Å molecular sieves, dichloroethane:ether 1:1, 3 h, 89%. *ii*) 25 wt% NaOMe in MeOH, 55 °C, 6 h, 80%. *iii*) HF–pyridine, THF, 6 h, 80%. *iv*) trifluoroacetic acid:water (20:1), 10 min, 62%. *v*) $Pd(OAc)_2$, H_2, MeOH, 35%. *vi*) NIS, cat. TfOH, 4 Å molecular sieves, dichloroethane:ether 1:1, 10 min; *vii*) **22**, 4 Å molecular sieves, NIS, cat. TfOH, 4 Å molecular sieves, dichloroethane:ether 1:1, 6 h, 42% (over *vi* and *vii*). $R^1 = (CH_2)_8CO_2Me$.

the final coupling. These results emphasise the importance of all the protecting groups in the determination of the reactivity of the glycosyl donor, with even the remote 6-position sometimes having a decisive influence. Further investigations are in progress to quantify these results.

Coupling of pentasaccharide **24** with tetrasaccharide **22** was pleasingly high-yielding, giving the nonasaccharide **25** in 89% yield (Scheme 5). This success encouraged us to attempt a one-pot, block coupling of this nonasaccharide. Starting from **23** and **6** the pentasaccharide **24** was formed and, without isolation, directly treated with the tetrasaccharide **22** to yield **25** in an unoptimised 42% yield. This remarkable procedure cut the number of reaction vessels down to *five* for the assembly of the fully protected nonasaccharide **25** from the monosaccharide building blocks.

The global deprotection of **25** proved to be troublesome. Debenzoylation with catalytic sodium methoxide in methanol was a very slow process. This was overcome by using excess sodium methoxide at 55 °C for 6 hours to give **26** in an excellent 80% yield. Desilylation with TBAF led to selective monodesilylation; however, the use of HF–pyridine in THF allowed direct access to the doubly desilylated compound **27** in 80% yield. CDA deprotection was achieved by treating **27** with trifluoroacetic acid:water (20:1) for 10 minutes. The desired compound **28** was isolated in a 62% yield, which corresponds to 89% per CDA unit.[24] The integrity of the anomeric positions was confirmed by 500 MHz NMR spectroscopy, indicating that even the relatively sensitive, β-mannosidic bond had been retained ($^1J_{C,H} = 154.6$ Hz). The final step, the removal of fifteen benzyl groups from **28**, was problematic. Hydrogenolysis with catalytic palladium hydroxide on charcoal (Pearlman's catalyst) gave very slow debenzylation. Furthermore, we were unable to isolate material from these reactions. We believe that this was due to the high affinity of the product for the charcoal portion of the catalyst. This problem was circumvented by employing hydrogenolysis with palladium acetate catalysis. On exposure of a methanolic palladium acetate solution to a hydrogen atmosphere, highly reactive palladium black is produced in situ. Application of this procedure to the nonasaccharide **28** produced complete removal of all fifteen benzyl groups to give the target oligosaccharide **2** in only 24 hours. The production of minor by-products could, however, be observed. MALDI-TOF mass spectrometric analysis suggested that these were the products from competitive hydrogenation of the aromatic rings of the benzyl groups to give one or two cyclohexylmethyl ether substituents on the nonosaccharide framework. Unfortunately these products were produced in proportionally larger amounts on scale-up, consequently our best yield for pure product isolated from this process was only 35%. The target oligosaccharide was readily purified by reverse-phase chromatography on MCI® gel (CHP 20 P),[25] followed by filtration through Sephadex® G 10. The proton NMR spectrum of **2** is clearly consistent with the target molecule, showing the presence of nine anomeric protons (three of which are coincidental), the methyl group of the methyl ester and the characteristic resonances of the alkyl linking arm (Figure 1). Full assignment of the spectrum and conformational

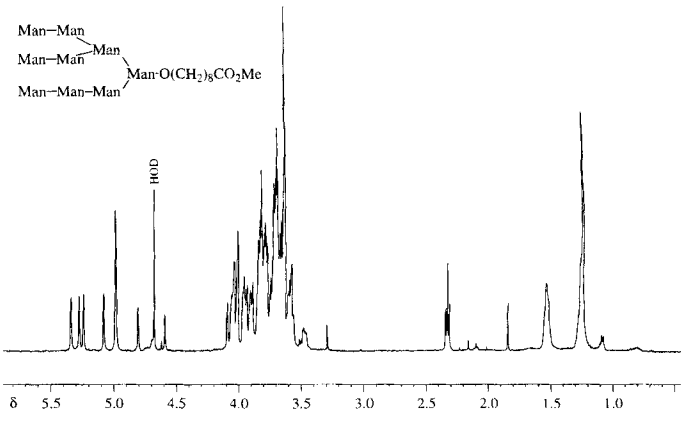


Figure 1. ^{1}H NMR (500 MHz) spectrum of **2**.

studies are in progress and will be reported in due course. The high-resolution mass spectrum, recorded using a MALDI source on an FT-ICR mass spectrometer, was also in full agreement with the structure of **2**.

Conclusion

We have reported an efficient synthesis of the nonasaccharide **2**, which is a model compound for a common glycan found on the viral coat of HIV-1. CDA methodology has allowed us to conveniently protect mannosides *and* tune the reactivity of glycosyl donors. With the appropriately protected monosaccharide precursors in hand, we were able to assemble the protected nonasaccharide by an iterative protocol involving only coupling steps. Only one protecting group manipulation was necessary. It was also possible to combine several of the glycosylation sequences into one-pot procedures, removing the need for tedious isolation of intermediates. This allowed the assembly of the nonasaccharide framework from the monosaccharide building blocks using only *five* reaction protocols. Although final debenzylation was problematic, our new CDA protecting group was easily removed and is clearly compatible with the synthesis of such large oligosaccharides. We believe that this synthesis demonstrates the power and effectiveness of designed, chemoselective, glycosylation sequences for the assembly of large oligosaccharides. Such strategies now rest at the heart of our approach to the controlled synthesis of biologically important carbohydrates.

Experimental Procedure

Materials and methods: ^{1}H NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on Bruker AM-200, Bruker AM-400 or Bruker DRX-500 spectrometers. Residual protic solvent $CHCl_3$ ($\delta = 7.26$) was used as the internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated, at 100 and 50 MHz on Bruker AM-400 and Bruker AM-200 spectrometers, respectively, using the resonance of $CDCl_3$ ($\delta = 77.0$) as the internal reference. Signals were assigned by means of 2D spectra (COSY, TOCSY, HMQC, HMBC). The numbering of the saccharide units are as indicated in the Schemes. Mass spectra were obtained on Kratos MS 890 MS, Kratos MALDI-2 and Bruker Apex 2 FT-ICR (4.7 T magnet) spectrometers at the Department of Chemistry, University of Cambridge. MALDI spectra were recorded using 2,5-dihydroxy benzoic acid as matrix. Microanalyses were determined in the microanalytical laboratories at the University of Cambridge. Optical rotations were measured with an Optical Activity AA-1000 polarimeter. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh) unless otherwise indicated. Analytical TLC was performed using precoated, glass-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet radiation or acidic ammonium molybdate(IV). Ether refers to diethyl ether and petrol refers to petroleum ether b.p. 40–60 °C, which was distilled prior to use. All reactions were carried out under an argon atmosphere and at room temperature unless otherwise stated. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl; dichloromethane, acetonitrile, dimethylformamide and toluene from calcium hydride. Other reagents and solvents were purified using standard procedures.[26]

Ethyl 2-*O*-benzoyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (6): Tetrabutylammonium fluoride (3 mL of a 1.1 M solution in tetrahydrofuran (THF)) was added to a stirred solution of **14**[18] (650 mg, 0.99 mmol) in THF (3 mL) and acetic acid (150 μL). After 6 h the reaction mixture was concentrated in vacuo, then extracted from saturated aqueous sodium bicarbonate (40 mL) solution with ethyl acetate (3 × 50 mL), dried (sodium sulfate), filtered and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate:petrol, 4:1) afforded **6** (280 mg, 0.67 mmol, 68%). $\alpha_D^{24} = +57$ ($c = 1.02$ in $CHCl_3$). ^{1}H NMR (200 MHz): $\delta = 7.25$–8.11 (m, 10H, Ar[H]), 5.44 (dd, $J_{2,3} = 3.3$ Hz, $J_{2,1} = 1.5$ Hz, 1H, 2-H), 5.39 (d, $^3J_{1,2} = 1.5$ Hz, 1H, 1-H), 4.87 (d, $^2J = 11.2$ Hz, 1H, PhCH_aH$_b$), 4.77 (d, $^2J = 11.2$ Hz, 1H, PhCH$_a$$H_b$), 4.21 (ddd, $^3J_{3,4} = 9.1$ Hz, $^3J_{3,OH} = 4.0$ Hz, $^3J_{3,2} = 3.3$ Hz, 1H, 3-H), 4.09 (ddd, $^3J_{5,4} = 9.7$ Hz, $^3J_{5,6a} = 3.4$ Hz, $^3J_{5,6b} = 3.0$ Hz, 1H, 5-H), 3.95 (dd, $^3J_{4,5} = 9.7$ Hz, $^3J_{4,3} = 9.1$ Hz, 1H, 4-H), 3.85–3.93 (m, 2H, 6-H), 2.54–2.71 (m, 2H, SCH$_2$), 2.24 (d, $^3J_{OH,3} = 4.0$ Hz, 1H, 3-OH), 1.92 (t, $^3J_{OH,6} \approx 4.0$ Hz, 1H, 6-OH), 1.29 (t, $^3J = 7.4$ Hz, 3H, CH$_3$). ^{13}C NMR (100 MHz): $\delta = 165.99$ (C=O), [138.00, 129.55] (*ipso*-C$_{arom.}$), [133.25, 129.72, 128.38 (2×), 128.00, 127.83] (C$_{arom.}$), 82.30 (C-1), [75.38, 74.79, 72.08, 70.92] (C-2, C-3, C-4, C-5), 74.79 (PhCH$_2$), 61.76 (C-6), 25.48 (CH$_2$S), 14.74 (CH$_3$). MS (EI): *m/z* (%): 418 (0.1) [M$^+$], 357 (29) [(M − SEt)$^+$]; HRMS (EI): calcd for $C_{22}H_{26}O_6S$ (M^+) 418.1450, found 418.1447. $C_{22}H_{26}O_6S \cdot 1/2\,H_2O$ (427.1): calcd C 61.81, H 6.37; found C 61.68, H 6.09.

8-(Methoxycarbonyl)octyl 2,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-mannoside (9):

*Formation of **17***: $TiBr_4$ (1.75 g, 4.7 mmol) was added to a stirred solution of **16**[19] (1.91 g, 3.9 mmol) in dichloromethane (DCM) (34 mL) and ethyl acetate (3.4 mL). After 3 h toluene (72 mL), acetonitrile (9.2 mL) and sodium acetate (18.5 g, 226 mmol) were added and stirring was continued until the mixture was completely decolourised. The suspension was filtered through a pad of Celite®, concentrated under reduced pressure and azeotroped with toluene (2 × 30 mL). The labile anomeric bromide was dissolved in toluene (6.2 mL) and added dropwise to a mixture of 8-methoxycarbonyloctanol (940 mg, 4.9 mmol), silver silicate (2.91 g), 4 Å molecular sieves (1.86 g) and DCM (22 mL), which had previously been stirred at −40 °C for 2 h. The temperature was slowly increased over 3 d (24 h at −40 °C, 24 h at −30 °C, 12 h at −15 °C and 12 h at 0 °C). Filtration through a pad of Celite®, concentration in vacuo and purification by flash column chromatography (hexane:ether, 4:1 to 2:1) gave the desired product **17** in 79% yield (1.89 g, 3.09 mmol). $\alpha_D^{24} = -42.7$ ($c = 5.08$ in $CHCl_3$). ^{1}H NMR (500 MHz): $\delta = 7.24$–7.48 (m, 10H, Ar[H]), 5.82–5.96 (m, 2H, 2 × allyl 2′-H), 5.16–5.30 (m, 4H, 4 × allyl 3′-H), 4.97 (d, $^2J = 12.5$ Hz, 1H, PhCH_aH$_b$-[2]), 4.92 (d, $^2J = 10.8$ Hz, 1H, PhCH_aH$_b$-[4]), 4.87 (d, $^2J = 12.5$ Hz, 1H, PhCH$_a$$H_b$-[2]), 4.59 (d, $^2J = 10.8$ Hz, 1H, PhCH$_a$$H_b$-[4]), 4.36 (s, 1H, 1-H), 3.91–4.10 (m, 5H, 4 × allyl 1′-H and OCH_aH$_b$ linker), 3.84 (d, $^3J_{2,3} = 2.9$ Hz, 1H, 2-H), 3.79 (t, $^3J_{4,3} = {}^3J_{4,5} = 9.7$ Hz, 1H, 4-H), 3.77 (dd, $^2J_{6a,6b} = 10.8$ Hz, $^3J_{6a,5} = 1.6$ Hz, 1H, 6-H$_a$), 3.67 (dd, $^2J_{6b,6a} = 10.8$ Hz, $^3J_{6b,5} = 6.2$ Hz, 1H, 6-H$_b$), 3.66 (s, 3H, OMe), 3.37–3.42 (m, 3H, 3-H, 5-H, OCH_aH$_b$ linker), 2.30 (t, $^3J = 7.6$ Hz, 2H, CH_2C=O), 1.59–1.64, 1.26–1.38 (m, 12H, 6 × CH$_2$ linker). ^{13}C NMR (100 MHz): $\delta = 174.20$ (C=O), [138.83, 138.54] (*ipso*-C$_{arom.}$), [135.01, 134.76] (=CH), [128.29, 128.03 (2×), 127.96, 127.60, 127.26] (C$_{arom.}$), 116.70 (=CH$_2$), 101.60 (C-1, $^1J_{C,H} = 153$ Hz), 82.30 (C-3), 75.87 (C-5), 75.09 (PhCH$_2$-[4]), 73.60 (PhCH$_2$-[2]), 74.94 (C-4), 73.53 (C-2), [72.41, 70.45] (OCH$_2$ allyl), [69.88, 69.79] (C-6 and OCH$_2$ linker), 51.36 (OCH$_3$), 34.04 (CH$_2$C=O), [29.62, 29.19, 29.16, 29.04, 26.03, 24.88] (6 × CH$_2$ linker). MS (EI): *m/z* (%) = 597 (0.8) [(M − OMe)$^+$], 569 (0.1), 519 (5), 422 (4), 331 (8), 91 (100); HRMS (EI) calcd for $C_{35}H_{47}O_7$ [(M − OMe)$^+$] 579.3322, found 579.3307.

*Formation of **18***: Deallylation of **17** was performed with *p*-toluenesulfonic acid (251 mg, 1.32 mmol) and 10% Pd/C (707 mg) in water (16.5 mL) and methanol (33.0 mL) for 4 h at 60 °C. The suspension was filtered through a pad of Celite®, concentrated and further purified by flash column chromatography (ether:hexane, 1:1 to 3:1). Compound **18** was isolated in 86% yield (1.42 g, 2.67 mmol), the analytical data being in full agreement with that previously reported.[20] ^{13}C NMR (100 MHz): $\delta = 174.29$ (C=O), [138.28, 138.25] (*ipso*-C$_{arom.}$), [128.57, 128.48, 128.27, 128.12, 128.00, 127.87] (C$_{arom.}$), 101.89 (C-1), 78.65 (C-2), 76.83 (C-4), 75.33 (C-5), 75.06 (PhCH$_2$-[4]), 74.87 (PhCH$_2$-[2]), 74.15 (C-3), 70.29 (OCH$_2$ linker), 62.59 (C-6), 51.48 (OCH$_3$), 34.08 (CH$_2$C=O), [29.68, 29.20 (2×), 29.08, 26.05, 24.92] (6 × CH$_2$ linker).

*Formation of **9***: *tert*-Butyldiphenylsilyl chloride (0.56 g, 2.19 mmol) and imidazole (293 mg, 4.25 mmol) were added to **18** (964 mg, 1.81 mmol) dissolved in THF (12 mL). After 2 h the reaction mixture was diluted with ether (100 mL), washed sequentially with water (50 mL), saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (ether:hexane, 1:1) furnished **9** (1.23 g, 1.60 mmol, 88%). $\alpha_D^{26} = -37.5$ ($c = 1.74$ in $CHCl_3$). ^{1}H NMR (500 MHz):

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δ = 7.79 (d, ^3J = 6.8 Hz, 2H, Ar[H]), 7.72 (d, ^3J = 6.8 Hz, 2H, Ar[H]), 7.25–7.45 (m, 16H, Ar[H]), 5.11 (d, ^2J = 11.7 Hz, 1H, PhCH_aH_b-[2]), 4.89 (d, ^2J = 11.0 Hz, 1H, PhCH_aH_b-[4]), 4.66 (d, ^2J = 11.7 Hz, 1H, PhCH_aH_b-[2]), 4.59 (d, ^2J = 11.0 Hz, 1H, PhCH_aH_b-[4]), 4.51 (s, 1H, 1-H), 3.94–4.00 (m, 3H, 6-$H_{a,b}$, OCH_aH_b linker), 3.85 (d, $^3J_{2,3}$ = 2.3 Hz, 1H, 2-H), 3.71–3.75 (m, 2H, 3-H, 4-H), 3.66 (s, 3H, OMe), 3.46 (dt, ^2J = 9 Hz, ^3J = 6.6 Hz, 1H, OCH_aH_b linker), 3.31–3.36 (m, 1H, 5-H), 2.57 (d, ^3J = 9.8 Hz, 1H, OH), 2.31 (t, ^3J = 7.5 Hz, 2H, CH_2C=O), 1.30–1.67 (m, 12H, 6 × CH_2 linker), 1.06 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz): δ = 174.21 (C=O), [138.69, 138.49, 133.91, 133.46] (*ipso*-$C_{arom.}$), [135.68, 135.58, 129.49, 128.31, 127.94, 127.88, 127.58, 127.49] ($C_{arom.}$), 101.55 (C-1), 77.79 (C-2), 76.79 (C-4), 76.18 (C-5), 74.76 (C-3), [74.48, 74.05] (CH_2Ph), 69.55 (OCH_2 linker), 63.32(C-6), 51.37 (OCH_3), 34.04 (CH_2C=O), [29.71, 29.19 (2×), 29.06, 26.15, 24.91] (6 × CH_2 linker), 26.95 (C[CH_3]$_3$), 19.30 (C[CH_3]$_3$). MS (MALDI-TOF): *m/z* (%): 792 (10) [$(M+Na)^+$]. $C_{46}H_{60}O_8Si$ (769.06): calcd C 71.84, H 7.86; found C 71.54, H 7.82.

(1′S,2′S)-Phenyl 2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-3*O*,4*O*-(1′,2′-dimethoxycyclohexan-1′,2′-diyl)-1-seleno-α-D-mannopyranoside (23): A solution of NIS (600 mg, 2.6 mmol) in 1,2-dichloroethane (DCE, 13 mL) and ether (9 mL) containing triflic acid (20 μL of a 3% stock solution of TfOH in DCE) was transferred to a prestirred (2 h) suspension of **3** (1.62 g, 2.3 mmol), **4** (1.25 g, 2.50 mmol), 4 Å molecular sieves (2.5 g), ether (25 mL) and DCE (25 mL). Stirring was continued for 5 min. The mixture was filtered through a pad of Celite® and the residue washed with DCM (3 × 50 mL). The filtrate was washed with 10% aqueous sodium thiosulfate (100 mL), saturated aqueous sodium bicarbonate solution (50 mL) and water (50 mL), and dried over sodium sulfate. Concentration in vacuo yielded the crude product, which was purified by flash column chromatography (hexane:ether, 19:1 to 3:1) furnishing **23** (1.31 g, 1.07 mmol) in 46% yield. α_D^{32} = + 87.2 (*c* = 1.27 in $CHCl_3$). ^{1}H NMR (500 MHz): δ = 7.11–7.68 (m, 35H, Ar[H]), 5.82 (s, 1H, 1-H), 5.55 (s, 1H, 1-H′), 4.83 (d, ^2J = 10.8 Hz, 1H, PhCH_aH_b-[4′]), 4.79 (d, ^2J = 12.5 Hz, 1H, PhCH_aH_b-[2′]), 4.61 (d, ^2J = 12.1 Hz, 1H, PhCH_aH_b-[6′]), 4.60 (d, ^2J = 12.5 Hz, 1H, PhCH_aH_b-[2′]), 4.41–4.50 (m, 6H, 2-H, 4-H, PhCH_aH_b-[3′], PhCH_aH_b-[4′], PhCH_aH_b-[6′]), 4.20 (dd, $^3J_{3,4}$ = 10.4 Hz, $^3J_{3,2}$ = 2.5 Hz, 1H, 3-H), 4.19 (m_c, 1H, 5-H), 3.96–4.01 (m, 2H, 2′-H, 6-H_a), 3.97 (t, $^3J_{4',3'}$ = $^3J_{4',5'}$ = 9.7 Hz, 1H, 4′-H), 3.93 (dd, $^3J_{3',4'}$ = 9.7 Hz, $^3J_{3',2'}$ = 3.0 Hz, 1H, 3′-H), 3.82–3.86 (m, 2H, 5′-H, 6-H_b), 3.75 (dd, $^2J_{6a',6b'}$ = 10.6 Hz, $^3J_{6a',5'}$ = 4.8 Hz, 1H, 6′-H_a), 3.65 (dd, $^2J_{6b',6a'}$ = 10.6 Hz, $^3J_{6b',5'} \approx$ 0.5 Hz, 1H, 6′-H_b), 3.64 (s, 3H, OMe), 3.27 (s, 3H, OMe), 1.70–1.80 [4H], 1.35–1.56 [4H] (m, 4 × CH_2 CDA), 0.98 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz): δ = [138.64, 138.44, 138.33, 134.06, 132.91, 130.00] (*ipso*-$C_{arom.}$), [135.94, 135.41, 133.54, 129.51, 129.45, 129.09, 128.27, 128.25, 128.23, 128.19, 128.12, 127.97, 127.83, 127.60, 127.52, 127.42, 127.30] ($C_{arom.}$), [98.76, 98.50] (acetal-C CDA), 98.29 (C-1′), 85.77 (C-1), 79.76 (C-3′), 75.90 (C-2), 74.95 (2×, C-4′, PhCH_2-[4′]), 74.40 (C-2′), 74.32 (C-5), 73.20 (PhCH_2-[6′]), 71.88 (C-5′), [71.83, 71.79] (PhCH_2-[2′]/[3′]), 70.92 (C-3), 69.05 (C-6′), 63.84 (C-4), 61.84 (C-6), [47.06, 46.96] (2 × OMe CDA), [27.16, 27.00, 21.44, 21.33] (4 × CH_2 CDA) 26.84 (C[CH_3]$_3$), 19.31 (C[CH_3]$_3$). MS (FAB): *m/z* (%): 1190 (0.2) [$(M-OMe)^+$], 523 (1) [$C_{34}H_{35}O_5^+$]. $C_{70}H_{80}O_{12}$SeSi (1220.46): calcd. C 68.89, H 6.61; found C 68.80, H 6.57.

(1′S,2′S)-Ethyl 2-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-benzoyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-6-*O*-benzoyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-1-thio-α-D-mannopyranoside (20): A mixture of per-*O*-benzylated phenylseleno-α-D-mannopyranoside **3**[117] (357 mg, 0.526 mmol), CDA-protected mannose derivative **5**[112e–e] (247 mg, 0.439 mmol) and powdered 4 Å molecular sieves (800 mg) was stirred for 2.5 h in ether (3 mL) and DCE (3 mL). NIS (138 mg, 0.614 mmol) in ether (2 mL) and DCE (3 mL) containing triflic acid (30 μL of a 3% stock solution of TfOH in DCE) was transferred through a cannula into the mixture of the two sugars, whereupon a purple colour appeared. After 10 min a suspension of **8** (289 mg, 0.618 mmol) and 4 Å molecular sieves (400 mg) was added, followed by a second batch of NIS (158 mg, 0.702 mmol) and TfOH (30 μL of stock solution) in ether (2 mL) and DCE (3 mL). Within 1 h the reaction was complete and no disaccharide **19** could be detected by TLC.[112e] The suspension was filtered through a pad of Celite® into a 10% sodium thiosulfate solution (20 mL), DCM (50 mL) was added, the layers were separated and the aqueous phase repeatedly extracted with DCM (4 × 30 mL). The combined organic layers were dried with sodium sulfate, filtered and the solvent was removed in vacuo to provide the crude material. Flash column chromatography (hexane:ether, 3:1 to 1:1) furnished **20** (408 mg, 0.291 mmol, 67%). α_D^{25} = + 125 (*c* = 0.76 in $CHCl_3$). ^{1}H NMR (500 MHz): δ = [8.04 (dd, ^3J = 1.5, 7.2 Hz, 4H), 7.57 (t, ^3J = 7.4 Hz, 1H), 7.19–7.52 (m, 23H), 7.09–7.14 (m, 2H), (Ar[H])], 5.65 (brs, 1H, 1-H″), 5.33 (brs, 1H, 1-H), 5.29 (brs, 1H, 1-H′), 4.88 (d, ^2J = 11.0 Hz, 1H, PhCH_aH_b-[4]), 4.83 (d, ^2J = 12.7 Hz, 1H, PhCH_aH_b-[2]), 4.74 (d, ^2J = 12.2 Hz, 1H, PhCH_aH_b-[6]), 4.66 (d, *J* 12.7 Hz, 1H, PhCH_aH_b-[2]), 4.62 (dd, $^2J_{6b',6a'}$ = 13.8, $^3J_{6b',5'}$ = 4.2 Hz, 1H, 6-H_b), 4.55 (dd, $^2J_{6b',6a'}$ = 11.8, $^3J_{6b',5'}$ = 1.5 Hz, 1H, 6-H_b′), 4.51 (d, ^2J = 11.5 Hz, 1H, PhCH_aH_b-[3]), 4.50 (d, ^2J = 11.0 Hz, 1H, PhCH_aH_b-[4]), 4.46 (d, ^2J = 11.5 Hz, 1H, PhCH_aH_b-[3]), 4.44 (d, ^2J = 12.2 Hz, 1H, PhCH_aH_b-[6]), 4.40–4.44 (m, 3H, 3-H, 6-H_a′ and 6-H_a), 4.36 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.5 Hz, 1H, 4-H), 4.29 (dd, $^3J_{3',4'}$ = 9.8 Hz, $^3J_{3',2'}$ = 2.1 Hz, 1H, 3-H′), 4.26 (t, $^3J_{4',3'}$ = $^3J_{4',5'}$ = 9.8 Hz, 1H, 4-H′), 4.23 (t, $^3J_{4'',3''}$ = $^3J_{4'',5''}$ = 9.8 Hz, 1H, 4-H″), 4.20 (brd, $^3J_{2',3'}$ = 2.1 Hz, 1H, 2-H′), 4.17 (br, 1H, 2-H), 4.12–4.17 (m, 2H, 5-H′ and 5-H), 4.00 (br, 1H, 2-H″), 3.96 (dd, $^3J_{3'',4''}$ = 9.5 Hz, $^3J_{3'',2''}$ = 3.1 Hz, 1H, 3-H″), 3.83 (dd, $^2J_{6b'',6a''}$ = 10.6 Hz, $^3J_{6b'',5''}$ = 2.5 Hz, 1H, 6-H_b″), 3.75 (brd, $^3J_{5'',4''}$ = 9.8 Hz, 1H, 5-H″), 3.68 (brd, $^2J_{6a'',6b''}$ = 10.6 Hz, 1H, 6-H_a″), [3.08, 3.09, 3.12, 3.16] (4 × s, 4 × 3H, 4 × OMe), 2.61 (m, 2H, SCH_2), 1.21–1.80 (m, 16H, 8 × CH_2 CDA), 1.25 (t, ^3J 7.4 Hz, 3H, SCH_2CH_3). ^{13}C NMR (100 MHz) [166.40, 166.31] (2 × C=O), [138.98, 138.67, 138.27, 133.04, 132.97, 130.14, 129.87, 129.69, 129.53, 128.44, 128.34, 128.25, 128.14, 127.91, 127.61, 127.55, 127.40, 127.29] ($C_{arom.}$), [98.71 (2×), 98.68, 98.64] (4 × acetal-C CDA), 99.95 (C-1′), 97.88 (C-1″), 84.10 (C-1), 79.87 (C-3″), 74.85 (PhCH_2-[4]), 74.73 (C-2), 74.49 (C-2″), 74.37 (C-4″), 73.62 (PhCH_2-[6]), 73.03 (C-2′), 72.08 (C-5″), 71.95 (PhCH_2-[3]), 71.79 (PhCH_2-[2]), 70.12 (C-5′), 69.86 (C-5), 69.56 (C-3′), 69.36 (C-3), 68.50 (C-6″), 64.68 (C-4′), 64.55 (C-4), 63.36 (C-6′), 63.07 (C-6), [46.96, 46.91, 46.81, 46.78] (4 × OMe), [27.26, 26.98, 26.94, 26.87] (4 × CH_2 CDA), 25.45 (SCH_2), [21.44 (2×), 21.33, 21.11] (4 × CH_2 CDA), 15.04 (SCH_2CH_3). MS (MALDI-TOF): *m/z* (%): 1420.5 (20) [$M+Na^+$]. $C_{78}H_{92}O_{21}S \cdot H_2O$: calcd. C 66.18, H 6.69; found: C 66.33, H 6.59.

(1′S,2′S)-8-(Methoxycarbonyl)octyl 3-*O*-(2-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-benzoyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-6-*O*-benzoyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-β-D-mannopyranoside (22): *Formation of* ***21***: Compounds **9** (0.62 g, 0.81 mmol) and **20** (1.042 g, 0.74 mmol) and 4 Å molecular sieves (3 g) in DCM (20 mL) were stirred at room temperature in the dark for 2 h. 2,6-Di-*tert*-butylpyridine (212 μL, 0.94 mmol) and silver triflate (1.0 g, 3.89 mmol) were added. After 30 min bromine (1.48 mL of 0.5 M stock solution in DCM, 0.74 mmol) was syringed into the mixture. Stirring was continued for 3 d, after which time the suspension was filtered through a pad of Celite® and the residue washed with DCM (3 × 40 mL). Concentration and purification by flash column chromatography (hexane:ether, 3:1 to 1:1) furnished slightly impure **21** (942 mg, 0.45 mmol, 60%). ^{1}H NMR (500 MHz): δ = 7.09–8.02 (m, 50H, Ar-[H]), 5.55 (s, 1H, 1a-H), 5.31 (s, 1H, 1b-H), 5.20 (s, 1H, 1c-H), 5.06 (d, ^2J = 12.1 Hz, 1H, PhCH_aH_b-[2d]), 4.89 (d, ^2J = 10.8 Hz, 1H, PhCH_aH_b-[4a]), 4.88 (d, ^2J = 12.6 Hz, 1H, PhCH_aH_b-[2d]), 4.81 (d, ^2J = 12.6 Hz, 1H, PhCH_aH_b-[2a]), 4.75 (d, ^2J = 11.2 Hz, 1H, PhCH_aH_b-[4d]), 4.72 (d, ^2J = 12.2 Hz, 1H, PhCH_aH_b-[6a]), 4.68 (d, ^2J = 12.6 Hz, 1H, PhCH_aH_b-[2a]), 4.54 (brd, $^2J_{6a,6b}$ = 11.2 Hz, 1H, 6c-H_a), 4.54 (d, ^2J = 10.8 Hz, 1H, PhCH_aH_b-[4a]), 4.49 (d, ^2J = 11.2 Hz, 1H, PhCH_aH_b-[4d]), 4.46 (s, 2H, PhCH_aH_b-[3a]), 4.43 (d, ^2J = 12.2 Hz, 1H, PhCH_aH_b-[6a]), 4.34 (s, 1H, 1d-H), 4.27-4.33 (m, 3H, 3c-H, 4b-H, 6b-H_a), 4.24 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.7 Hz, 1H, 4a-H), 4.22 (br, 1H, 2b-H), 4.20–4.26 (m, 3H, 3b-H, 4c-H, 6c-H_b), 4.12 (br, 1H, 2c-H), 4.11 (b, 1H, 2a-H), 4.01 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.6 Hz, 1H, 4d-H), 3.94–4.01 (m, 4H, 3a-H, 5b-H, 5c-H, 6b-H_b), 3.89 (dt, ^2J = 9 Hz, ^3J = 6.6 Hz, 1H, OCH_aH_b linker), 3.86 (br, 1H, 2d-H), 3.82-3.85 (m, 2H, 5a-H, 6a-H_a), 3.81 (m_c, 2H, 6d-$H_{a,b}$), 3.73 (dd, $^3J_{3,4}$ = 9.7 Hz, $^3J_{3,2}$ = 3.0 Hz, 1H, 3d-H), 3.67–3.69 (m, 1H, 6a-H_b), 3.67 (s, 3H, OMe), 3.35 (dt, ^2J = 9 Hz, ^3J = 6.6 Hz, 1H, OCH_aH_b linker), 3.17 (dt, $^3J_{5,4}$ = 9.7 Hz, $^3J_{5,6a} \approx {}^3J_{5,6b} \approx$ 2.5 Hz, 1H, 5d-H), [3.12, 3.10, 3.08, 2.94] (4 × s, 4 × 3H, 4 × OMe CDA), 2.30 (t, ^3J = 7.6 Hz, 2H, CH_2C=O), 0.87–1.71 (m, 28H, 8 × CH_2 CDA, 6 × CH_2 linker), 1.00 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz): δ = 174.31 (C=O), [166.29, 166.12] (PhC=O), [138.99, 138.85, 138.72, 138.40, 137.81, 135.91, 135.58, 133.91, 133.44, 133.00, 132.87, 130.16, 129.98, 129.56, 129.43, 128.51, 128.43, 128.33, 128.23, 128.19, 128.15, 127.91, 127.82, 127.77, 127.73, 127.59, 127.48, 127.41, 127.29, 127.22] ($C_{arom.}$/signals overlap), 101.65 (C-1d), 100.37 (C-1c), 100.35 (C-1b), 98.56 (C-1a), [98.76 (2×), 98.50 (2×)] (acetal-C CDA), 80.58 (C-3d), 80.20 (C-3a), 77.26

(C-2d), 76.62 (C-5d), 75.15 (C-4d), 74.97 (C-2a), 74.96 (C-2c), 74.95 (PhCH$_2$-[4a]), 74.95 (PhCH$_2$-[4d]), 74.73 (C-2b), 74.50 (C-4a), 73.70 (PhCH$_2$-[2d]), 73.57 (PhCH$_2$-[6a]), 72.21 (C-5a), 71.98 (PhCH$_2$-[2a]), 71.79 (PhCH$_2$-[3a]), 69.94 (C-5b), 69.63 (C-5c), 69.37 (C-3b), 69.11 (C-3c), 68.73 (C-6a), 64.48 (C-4c), 63.96 (C-4b), 63.38 (C-6c), 63.01 (C-6d), 62.62 (C-6b), 51.46 (OMe), [46.83, 46.71, 46.62] (4 × OMe CDA), 34.13 (*C*H$_2$C=O), [29.87, 29.37, 29.28, 29.15, 27.25, 26.99, 26.25, 24.99, 21.43] (8 × *C*H$_2$ CDA, 6 × *C*H$_2$ linker/signals overlap), 26.74 (C[*C*H$_3$]$_3$), 19.29 (*C*[CH$_3$]$_3$). MS (MALDI-TOF): *m/z* (%) = 2127.9 [*M* + Na$^+$].

Formation of **22**: Compound **21** (370 mg, 175.8 μmol) was treated with TBAF (0.52 mL of a 1.1 M solution in THF) and acetic acid (17 μL) at room temperature for 12 h. The mixture was partitioned between aqueous sodium bicarbonate solution (30 mL) and DCM (70 mL), and the organic extracts were dried with sodium sulfate. Concentration in vacuo yielded the crude product, which was purified by flash column chromatography (ether:hexane, 1:1 to 2:1) to afford **22** (285 mg, 152.7 μmol, 87%). $\alpha_D^{26} = +65.5$ (*c* = 1.82 in CHCl$_3$). ^{1}H NMR (500 MHz): δ = 7.14–8.00 (m, 40H, Ar[H]), 5.56 (brs, 1H, 1a-H), 5.31 (brs, 1H, 1b-H), 5.22 (brs, 1H, 1c-H), 5.02 (d, ^2J = 12.0 Hz, 1H, PhC*H*$_a$H$_b$-[2d]), 4.90 (d, ^2J = 12.0 Hz, 1H, PhCH$_a$*H*$_b$-[2d]), 4.89 (d, ^2J = 10.8 Hz, 1H, PhC*H*$_a$H$_b$-[4a]), 4.82 (d, ^2J = 12.7 Hz, 1H, PhC*H*$_a$H$_b$-[2a]), 4.77 (d, ^2J = 11.6 Hz, 1H, PhC*H*$_a$H$_b$-[4d]), 4.72 (d, ^2J = 12.3 Hz, 1H, PhC*H*$_a$H$_b$-[6a]), 4.69 (d, ^2J = 12.7 Hz, 1H, PhCH$_a$*H*$_b$-[2a]), 4.54 (d, ^2J = 10.8 Hz, 1H, PhCH$_a$*H*$_b$-[4a]), 4.53 (dd, $^2J_{6a,6b}$ = 11.6 Hz, $^3J_{6a,5} \approx 1$ Hz, 1H, 6c-H$_a$), 4.48 (d, ^2J = 11.6 Hz, 1H, PhCH$_a$*H*$_b$-[4d]), 4.47 (br, 2H, PhC*H*$_a$*H*$_b$-[3a]), 4.44 (d, ^2J = 12.3 Hz, 1H, PhCH$_a$*H*$_b$-[6a]), 4.35 (brs, 1H, 1d-H), 4.32 (t, $^3J_{4,3} = {}^3J_{4,5}$ = 10.0 Hz, 1H, 4b-H), 4.32 (dd, $^2J_{6a,6b}$ = 11.6 Hz, $^3J_{6a,5}$ = 4.5 Hz, 1H, 6b-H$_a$), 4.29 (dd, $^3J_{3,4}$ = 10.3 Hz, $^3J_{3,2} \approx 2$ Hz, 1H, 3c-H), 4.20–4.25 (m, 5H, 3b-H, 4a-H, 6c-H$_b$, 2b-H, 4c-H), 4.12 (brd, $^3J_{2,3} \approx 2$ Hz, 1H, 2a-H), 4.11 (brd, $^3J_{2,3} \approx 2$ Hz, 1H, 2c-H), 3.96–4.04 (m, 3H, 6b-H$_b$, 3a-H, 5b-H), 3.92 (t, $^3J_{4,3} = {}^3J_{4,5}$ = 9.6 Hz, 1H, 4d-H), 3.84–3.93 (m, 5H, 5c-H, OC*H*$_a$H$_b$ linker, 2d-H, 6a-H$_a$, 5a-H), 3.74 (dd, $^3J_{3,4}$ = 9.6 Hz, $^3J_{3,2}$ = 2.6 Hz, 1H, 3d-H), 3.65–3.75 (m, 2H, 6d-H$_a$, 6a-H$_b$), 3.67 (s, 3H, OMe), 3.58 (dt, $^2J_{6b,6a} \approx 12$ Hz, $^3J_{6b,5} \approx J_{6b,OH} \approx 5$ Hz, 1H, 6d-H$_b$), 3.34 (dt, ^2J = 9 Hz, ^3J = 6.8 Hz, 1H, OCH$_a$*H*$_b$ linker), 3.16 (ddd, $^3J_{5,4}$ = 9.6 Hz, $^3J_{5,6b} \approx 5$ Hz, $^3J_{5,6a}$ = 3.3 Hz, 1H, 5d-H), [3.12, 3.09, 3.08, 2.96] (4 × s, 4 × 3H, 4 × OMe CDA), 2.31 (t, ^3J = 7.5 Hz, 2H, *C*H$_2$C=O), 2.00 (t, $^3J \approx 5$ Hz, 1H, 6d-OH), 1.21–1.80 (m, 28H, 6 × *C*H$_2$ linker, 8 × *C*H$_2$ CDA). ^{13}C NMR (100 MHz): δ = 174.31 (C=O), [166.23, 166.13] (PhC=O), [138.96, 138.86, 138.70, 138.40, 138.16, 137.55, 130.14, 130.02] (*ipso*-C$_{arom.}$), [133.05, 132.89, 129.54, 129.46, 128.64, 128.47, 128.27, 128.25, 128.20, 128.06, 127.84, 127.80, 127.74, 127.61, 127.55, 127.49, 127.43, 127.38, 127.31] (C$_{arom.}$), 101.72 (C-1d), 101.36 (C-1c), 100.48 (C-1b), 99.56 (C-1a), [98.69 (2×), 98.63, 98.55] (acetal-C CDA), [80.19, 80.13] (C-3a, C-3d), 76.63 (C-2d), 75.78 (C-5d), 75.15 (C-2c), 75.06 (C-4d), 74.99 (PhCH$_2$-[4a]), 74.94 (C-2a), 74.87 (PhCH$_2$-[4d]), 74.72 (C-2b), 74.50 (C-4a), 73.94 (PhCH$_2$-[2d]), 73.60 (PhCH$_2$-[6a]), 72.22 (C-5a), 71.98 (PhCH$_2$-[2a]), 71.80 (PhCH$_2$-[3a]), 70.24 (OCH$_2$ linker), 70.01 (C-5c), 69.72 (C-5b), 69.34 (C-3b), 69.01 (C-3c), 68.73 (C-6a), 64.44 (C-4c), 63.94 (C-4b), 63.28 (C-6c), 62.63 (C-6b), 62.09 (C-6d), 51.49 (OMe), [46.78 (2×), 46.72, 46.62] (OMe CDA), 34.11 (*C*H$_2$C=O), [29.75, 29.32, 29.24, 29.13, 26.09, 24.96] (6 × *C*H$_2$ linker), [27.27, 26.99, 26.94, 21.42, 21.21] (8 × *C*H$_2$ CDA/signals overlap). MS (MALDI-TOF): *m/z* (%): 1887.8 (53) [(*M* + Na)$^+$]. $C_{106}H_{128}O_{29}$: calcd. C 68.22, H 6.91; found: C 68.25, H 6.94.

(1′*S*,2′*S*)-Ethyl 3,6-di-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-2-*O*-benzoyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (24): Compounds **23** (0.95 g, 0.78 mmol) and **6** (0.16 g, 0.38 mmol) and 4 Å molecular sieves (2 g) were stirred in ether (6 mL) and DCE (6 mL). After 2 h NIS (0.18 g, 0.80 mmol) and TfOH (10 μL of a stock solution containing 30 μL TfOH in 1 mL DCE) in ether (6 mL) and DCE (6 mL) were added. After 5 min the mixture was filtered through a pad of Celite® and the filtrate immediately partitioned between DCM (70 mL) and 10% aqueous sodium thiosulfate (30 mL). After drying the extracted organic phase with sodium sulfate, filtration and concentration under reduced pressure gave the crude product. Flash column chromatography (petrol:ether, 9:1 to 7:3) furnished **24** (0.61 g, 0.24 mmol, 63%). $\alpha_D^{26} = +43.1$ (*c* = 1.13 in CHCl$_3$). ^{1}H NMR (500 MHz): δ = 7.10–8.01 (m, 70H, Ar[H]), 5.57 (s, 1H, 1a-H), 5.53 (d, $^3J_{1,2}$ = 1.4 Hz, 1H, 1d-H), 5.35 (s, 1H, 2c-H), 5.28 (s, 1H, 1c-H), 4.95 (s, 1H, 1b-H), 4.81 (s, 1H, 1e-H), 4.92 (d, ^2J = 11.4 Hz, 1H, PhC*H*$_a$H$_b$-[1]), 4.86 (d, ^2J = 10.8 Hz, 1H, PhC*H*$_a$H$_b$-[2]), 4.83 (d, ^2J = 10.9 Hz, 1H, PhC*H*$_a$H$_b$-[3]), 4.78 (d, ^2J = 12.6 Hz, 1H, PhC*H*$_a$H$_b$-[4]), 4.76 (d, ^2J = 12.5 Hz, 1H, PhC*H*$_a$H$_b$-[5]), 4.64 (d, ^2J = 12.1 Hz, 1H, PhC*H*$_a$H$_b$-[6]), 4.62 (d, ^2J = 12.6 Hz, 1H, PhCH$_a$*H*$_b$-[4]), 4.59 (d, ^2J = 12.5 Hz, 1H, PhCH$_a$*H*$_b$-[5]), 4.58 (d, ^2J = 12.1 Hz, 1H, PhC*H*$_a$H$_b$-[7]), 4.53 (d, ^2J = 11.4 Hz, 1H, PhCH$_a$*H*$_b$-[1]), 4.50 (d, ^2J = 10.8 Hz, 1H, PhCH$_a$*H*$_b$-[2]), 4.38–4.48 (m, 7H, PhCH$_a$*H*$_b$-[3], PhCH$_a$*H*$_b$-[6], PhC*H*$_a$H$_b$-[8], PhC*H*$_a$H$_b$-[9], 4b-H), 4.28–4.30 (m, 2H, 3e-H, PhCH$_a$*H*$_b$-[7]), 4.25 (dd, $^3J_{3,4}$ = 9.4 Hz, $^3J_{3,2} \approx 3$ Hz, 1H, 3c-H), 4.25 (t, $^3J_{4,3} = {}^3J_{4,5}$ = 9.1 Hz, 1H, 4e-H), 4.20 (ddd, $^3J_{5,4} \approx 9.5$ Hz, $^3J_{5,6a} \approx 4.5$ Hz, $^3J_{5,6b} \approx 1$ Hz, 1H, 5c-H), 4.00-4.13 (m, 7H, 3b-H, 2a-H, 2b-H, 2d-H, 2e-H, 4a-H, 4d-H), 3.95 (dd, $^3J_{3,4} \approx 9.2$ Hz, $^3J_{3,2} \approx 3.3$ Hz, 1H, 3d-H), 3.94 (dd, $^3J_{3,4} \approx 9.2$ Hz, $^3J_{3,2} \approx 3.2$ Hz, 1H, 3a-H), 3.90 (t, $^3J_{4,3} = {}^3J_{4,5}$ = 9.6 Hz, 1H, 4c-H), 3.47–3.86 (m, 12H, 5a-H, 5b-H, 5d-H, 5e-H, 6b-H$_{a,b}$, 6c-H$_{a,b}$, 6d-H$_{a,b}$, 6e-H$_{a,b}$), 3.55 (dd, $^2J_{6a,6b}$ = 10.8 Hz, $^3J_{6a,5}$ = 3.6 Hz, 1H, 6a-H$_a$), 3.31 (dd, $^2J_{6b,6a}$ = 10.8 Hz, $^3J_{6b,5} \approx 1$ Hz, 1H, 6a-H$_b$), [3.17, 3.07, 3.06, 2.89] (4 × s, 4 × 3H, 4 × OMe CDA), 2.50–2.62 (m, 2H, SC*H*$_2$), 1.25–1.79 (m, 16H, 8 × *C*H$_2$ CDA), 1.22 (t, ^3J = 7 Hz, 3H, SCH$_2$*C*H$_3$), [1.00, 0.96] (2 × s, 2 × 9H, 2 × *t*Bu). ^{13}C NMR (100 MHz): δ = 165.40 (PhC=O), [138.88, 138.81, 138.78, 138.76, 138.46, 137.79, 136.03, 135.92, 135.57, 135.51, 134.40, 134.03, 133.38, 133.16, 133.09, 129.94, 129.72, 129.55, 129.49, 129.37, 128.57, 128.48, 128.38, 128.28, 128.23, 128.21, 128.17, 128.01, 127.96, 127.91, 127.86, 127.79, 127.69, 127.59, 127.56, 127.49, 127.44, 127.39, 127.36, 127.30, 127.26, 127.23] (C$_{arom.}$/signals overlap), 101.51 (C-1b), 99.65 (C-1e), 98.37 (C-1a), 98.18 (C-1d). [98.71, 98.44, 98.29 (2×)] (4 × acetal-C CDA), 81.89 (C-1c), 80.07 (C-3a), 79.91 (C-3d), 77.67 (C-3c), 75.49 (C-4c), [75.04, 74.96, 74.75, 73.39, 73.30, 71.87, 71.83 (3×)] (9 × PhCH$_2$), [74.84, 74.75, 74.57, 74.48, 74.17] (C-2a, C-2b, C-2c, C-2d, C-2e, C-4a, C-4d; signals overlap), [73.15, 72.26, 72.07 (2×)] (C-5a, C-5b, C-5d, C-5e), 71.18 (C-5c), 70.16 (C-3e), 69.16 (C-3b), 69.08 (C-6d), 68.67 (C-6a), 65.94 (C-6c), 63.80 (C-4e), 62.99 (C-4b), 62.13 (C-6c), 61.49 (C-6b), [47.11, 47.01, 46.70, 46.40] (4 × OMe CDA), [27.28, 27.21, 27.02, 26.90] (4 × *C*H$_2$ CDA), [27.04, 26.83] (2 × [(CH$_3$)$_3$*C*]), 25.42 (*SCH*$_2$), 21.45 (4 × *C*H$_2$ CDA), [19.45, 19.32] (2 × [(CH$_3$)$_3$*C*]), 14.91 (SCH$_2$*C*H$_3$). MS (MALDI-TOF): *m/z* = 2566.1 [(*M* + Na)$^+$]. $C_{150}H_{174}O_{30}SSi_2$: calcd. C 70.79, H 6.89; found: C 70.68, H 6.97.

(1′*S*,2′*S*)-8-(Methoxycarbonyl)octyl 3-*O*-(2-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-benzoyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-6-*O*-benzoyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-6-*O*-(3,6-di-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-2-*O*-benzoyl-4-*O*-benzyl-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-β-D-mannopyranoside (25): Acceptor **22** (80 mg, 42.8 μmol), donor **24** (87 mg, 34.2 μmol), 4 Å molecular sieves (50 mg), DCE (240 μL) and ether (240 μL) were stirred for 2 h, before NIS (12 mg, 54.7 μmol) and TfOH (5 μL of stock solution containing 30 μL TfOH in 1 mL DCE) in ether (160 μL) and DCE (240 μL) were added. After 3 h TLC implied that the donor was consumed and the reaction was worked up. The mixture was filtered through a pad of Celite®, partitioned between DCM (20 mL) and 10% aqueous sodium thiosulfate (2 × 10 mL), and washed with saturated aqueous sodium bicarbonate solution. The organic extracts were dried with sodium sulfate. Concentration under reduced pressure afforded the crude product which was purified by flash column chromatography (hexane:ether, 3:1 to 1:1) to yield **25** (133 mg, 30.6 μL, 89%). $\alpha_D^{26} = +70.5$ (*c* = 0.38 in CHCl$_3$). Selected NMR data; ^{1}H NMR (500 MHz): δ = 5.57 (br, 2H, 1a-H, 1h-H), 5.52 (s, 1H, 1e-H), 5.35 (br, 2H, 2g-H, 1b-H), 5.16 (s, 2H, 1c-H, 1f-H), 4.86 (s, 1H, 1i-H), 4.73 (s, 1H, 1g-H), 4.25 (s, 1H, 1d-H). ^{13}C NMR (100 MHz): δ = 101.49 (C-1c), 101.26 (C-1d), 101.17 (C-1f), 100.21 (C-1b), 99.64 (C-1i), 98.3 (C-1a and C-1e), 98.07 (C-1h), 96.41 (C-1g), 80.87 (C-3d), 80.18, 80.04, 79.82 (C-3a, C-3e, C-3h), 77.81 (C-3g). MS (MALDI-TOF): *m/z* = 4384.7 [(*M* + K)$^+$]. $C_{254}H_{296}O_{59}Si_2 \cdot 2H_2O$: calcd. C 69.57, H 6.89; found: C 69.45, H 6.74.

One-pot procedure: Disaccharide **23** (102.5 mg, 84 μmol), **6** (12.4 mg, 29.6 μmol) and 4 Å molecular sieves (50 mg) were stirred in DCE (150 μL) and ether (150 μL). After 3 h NIS (19.4 mg, 89 μmol) and TfOH (7 μL of the stock solution) in DCE (0.6 mL) and ether (0.4 mL) were added. The formation of the pentasaccharide **24** was complete within 10 min as judged by TLC. A prestirred (2 h) suspension of **22** (70 mg, 37.5 μmol) and 4 Å molecular sieves (25 mg) in DCE (120 μL) and ether (120 μL) was added, followed by NIS (9.7 mg, 44.5 μmol) and TfOH (7 μL of the stock solution) in DCE (0.3 mL) and ether (0.2 mL). Over the next 5 h four portions of TfOH (4 × 5 μL) were added. After 6 h no further reaction could be observed and the reaction mixture was worked up as described above. The nonasaccharide **25** (data: see above) was isolated in a 42% yield (54 mg, 12.4 μmol).

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(1′S,2′S)-8-(Methoxycarbonyl)octyl 3-*O*-(2-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-6-*O*-(3,6-di-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-4-*O*-benzyl-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-β-D-mannopyranoside (26): Compound **25** (551 mg, 0.126 mmol) was dissolved in THF (4 mL). Methanol (20 mL) and sodium methoxide in methanol (2 mL of a 25 wt% solution) were added and the mixture heated to 55 °C. After 6 h Amberlite® was added and the mixture stirred for another 10 min. Filtration and extensive washing of the solid residue with DCM furnished the crude product after concentration in vacuo. **26** (405 mg, 0.1 mmol, 80%) was isolated after flash column chromatography (hexane:ether, 2:1 to 1:4). $\alpha_D^{26} = +58.8$ ($c = 4.8$ in $CHCl_3$). Selected NMR data; ^{1}H NMR (500 MHz): $\delta = 5.59$ (s, 1H, 1h-H), 5.53 (s, 1H, 1a-H), 5.45 (s, 1H, 1e-H), 5.12 (s, 1H, 1f-H), 5.07 (s, 1H, 1c-H), 5.06 (s, 1H, 1b-H), 4.91 (s, 1H, 1i-H), 4.52 (s, 1H, 1g-H), 4.26 (s, 1H, 1d-H). ^{13}C NMR (100 MHz): $\delta = 101.57$ (C-1c), 101.30 (C-1d), 100.73 (C-1b), 100.63 (C-1f), 99.93 (C-1i), 99.63 (C-1g), 98.19 (C-1e), 98.04 (2×) (C-1a, C-1h). MS (MALDI-TOF): $m/z = 4072.9$ $[(M+K)^+]$. $C_{233}H_{284}O_{56}Si_2$: calcd. C 69.32, H 7.09; found: C 69.12, H 7.15.

(1′S,2′S)-8-(Methoxycarbonyl)octyl 3-*O*-(2-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-6-*O*-(3,6-di-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-3*O*,4*O*-[1′,2′-dimethoxycyclohexan-1′,2′-diyl]-α-D-mannopyranosyl)-4-*O*-benzyl-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-β-D-mannopyranoside (27): **26** (220 mg, 54 μmol) was treated for 6 h with HF–pyridine (10 mL of a stock solution containing 3.8 mL HF · pyridine, 14 mL pyridine and 40 mL THF). Saturated aqueous sodium bicarbonate solution (60 mL) was added and the mixture extracted with DCM (3 × 50 mL). The organic layer was dried with sodium sulfate, filtered and concentrated under reduced pressure. After flash column chromatography (ethyl acetate:hexane, 1:1 to 3:1) **27** (156 mg, 44 μmol, 80%) was obtained. $\alpha_D^{26} = +79.7$ ($c = 1.28$ in $CHCl_3$). ^{1}H NMR (500 MHz): $\delta = 7.11-7.47$ (m, 75H, Ar[H]), 5.53 (s, 1H, 1a-H), 5.51 (s, 1H, 1h-H), 5.47 (s, 1H, 1e-H), 5.13 (s, 1H, 1f-H), 5.09 (s, 1H, 1c-H), 5.06 (s, 1H, 1b-H), 5.01 (s, 1H, 1i-H), 4.98 (d, $^2J = 12.0$ Hz, 1H, PhCH_aH$_b$-[2d]), 4.91 (d, $^2J = 10.6$ Hz, 1H, PhCH_2), 4.89 (d, $^2J = 10.5$ Hz, 1H, PhCH_2), 4.48–4.84 (m, 24H, PhCH_2), 4.68 (s, 1H, 1g-H), [4.45 (d, $^2J = 12.3$ Hz, 1H), 4.43 (d, $^2J = 12.6$ Hz, 1H), 4.34 (d, $^2J = 12.3$ Hz, 1H)] {PhCH_aH$_b$-[6a]-, PhCH_aH$_b$-[6e] and PhCH_aH$_b$-[6h]}, 4.32 (s, 1H, 1d-H), 4.26 (br, 1H, 2b-H), 4.18–4.26 (m, 8H, 3b-H, 3c-H, 3f-H, 3i-H, 4a-H, 4b-H, 4c-H, 4i-H), 4.17 (br, 1H, 2i-H), 4.12 (br, 1H, 2a-H), 4.10 (t, $^3J_{4,5} \approx {}^3J_{4,3} \approx 9.5$ Hz, 1H, 4f-H), 4.08 (br, 1H, 2h-H), 4.05 (br, 1H, 2f-H), 4.04 (br, 1H, 2e-H), 3.95–4.05 (m, 6H, 3a-H, 3g-H, 3h-H, 4e-H, 4h-H, 5f-H), 3.94 (br, 1H, 2c-H), 3.93 (dd, $^3J_{3,4} \approx 10$ Hz, $^3J_{3,2} \approx 3$ Hz, 1H, 3e-H), 3.89 (t, $^3J_{4,5} \approx {}^3J_{4,3} \approx 9.5$ Hz, 1H, 4g-H), 3.85 (br, 1H, 2g-H), 3.80 (t, $^3J_{4,5} \approx {}^3J_{4,3} \approx 10$ Hz, 1H, 4d-H), 3.66 (s, 3H, OMe), 3.50–3.88 (m, 25H, 2d-H, 3d-H, 5a-H, 5b-H, 5c-H, 5e-H, 5g-H, 5h-H, 5i-H, 6a-H$_{a,b}$, 6c-H$_{a,b}$, 6d-H$_{a,b}$, 6e-H$_a$, 6f-H$_{a,b}$, 6g-H$_{a,b}$, 6h-H$_{a,b}$, 6i-H$_{a,b}$, linker CH_aH$_b$), 3.47 (dd, $^2J_{6a,6b} \approx 12$ Hz, $^3J_{6a,5} \approx 1.5$ Hz, 1H, 6b-H$_a$), 3.35 (br d, $^2J_{6b,6a} \approx 12$ Hz, 1H, 6e-H$_b$), 3.31–3.36 (m, 1H, linker CH$_a$H$_b$), 3.31 (dd, $^2J_{6b,6a} \approx 12$ Hz, $^3J_{6b,5} \approx 1.5$ Hz, 1H, 6b-H$_b$), 3.25–3.29 (m, 1H, 5d-H), [3.23, 3.21, 3.17, 3.16, 3.14, 3.12, 3.11, 3.10] (8 × s, 8 × 3H, 8 × OMe CDA), 2.28 (t, $^3J = 7.6$ Hz, 2H, CH_2C=O), 1.21–1.75 (m, 44H, 6 × CH_2 linker and 16 × CH_2 CDA). ^{13}C NMR (100 MHz): $\delta = 174.28$ (C=O), [138.93, 138.78, 138.73 (2×), 138.66, 138.62, 138.56, 138.52, 138.49, 138.42, 138.38, 138.26, 138.08, 138.74] (*ipso* C$_{arom.}$), 127.14–128.50 (C$_{arom.}$, overlapping signals), [98.69, 98.62, 98.43, 98.38] (acetal-C CDA, overlapping signals), 101.63 (C-1c), 101.46 (C-1d), 100.68 (C-1b), 100.47 (C-1f), 99.83 (C-1g, C-1i), 98.51 (C-1e), 98.10 (C-1a), 97.91 (C-1h), 80.96 (C-3d), 79.68 (C-3a), 79.44 (C-3e), 79.19 (C-3g and C-3h), 77.21 (C-2d), 76.66 (C-2c), 75.24 (C-4d), 74.50–75.12 (overlapping signals of: 4 × PhCH_2, C-2a, C-2b, C-2e, C-2f, C-2h, C-2i, C-4a, C-4e, C-4h, C-5d), 74.20 (C-4g), 73.82 (PhCH_2-[2d]), [73.50, 73.44, 73.15] (PhCH_2-[6a], PhCH_2-[6e] and PhCH_2-[6h]), [71.1–72.2, 69.60] (overlapping signals of: 7 × PhCH_2, C-2g, C-5a, C-5b, C-5c, C-5e, C-5f, C-5g, C-5h and C-5i), [69.86, 69.80] (C-6h, OCH_2 linker), [69.48, 69.31, 69.14] (C-3b, C-3f, C-3i), 68.92 (C-6a), 68.66 (C-6e), 68.49 (C-3c), 66.30 (C-6d), 65.36 (C-6g), 64.38 (C-4f), [63.78 (2×), 63.61] (C-4b, C-4c, C-4i), 61.13 (3×, C-6c, C-6f, C-6i), 60.75 (C-6b), 51.39 (OMe), [46.86, 46.79, 46.73, 46.72, 46.69, 46.65, 46.61, 46.51] (OMe CDA), 34.05 (CH_2C=O), [29.65, 29.25, 29.14, 29.06, 27.19, 26.88, 24.90, 21.32] (overlapping signals of 6 × CH_2 linker and 16 × CH_2 CDA). MS (MALDI-TOF): $m/z = 3580.4$ $[(M+Na)^+]$. $C_{201}H_{248}O_{56} \cdot 4H_2O$: calcd. C 66.47, H 7.10; found: C 66.31, H 6.81.

8-(Methoxycarbonyl)octyl 3-*O*-(2-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-6-*O*-(3,6-di-*O*-(2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-4-*O*-benzyl-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-β-D-mannopyranoside (28): Compound **27** (88mg, 24.7 μmol) was treated with trifluoroacetic acid and water (8.8 mL of a 20:1 solution) for 10 min. The reaction mixture was diluted with DCM (20 mL) and immediately poured into an ice-cold, vigorously stirred solution of saturated aqueous sodium bicarbonate (200 mL). The layers were separated, and the aqueous phase extensively extracted with ethyl acetate (5 × 50 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (100% ethyl acetate to 15% *iso*propanol in ethyl acetate) furnished slightly impure **28** (46 mg, 15.3 μmol, 62%). Selected NMR data; ^{1}H NMR (500 MHz, [D$_6$]acetone): $\delta = 5.43$ (d, $^1J_{C,H} = 169.8$ Hz, 1H, 1f-H), 5.37 (d, $^1J_{C,H} = 172.1$ Hz, 1H, 1c-H), 5.27 (d, $^1J_{C,H} = 170.3$ Hz, 1H, 1h-H), 5.22 (d, $^1J_{C,H} = 170.1$ Hz, 1H, 1a-H), 5.18 (d, $^1J_{C,H} = 171.3$ Hz, 1H, 1b-H), 5.15 (d, $^1J_{C,H} = 170.1$ Hz, 1H, 1e-H), 5.11 (d, $^1J_{C,H} = 170.6$ Hz, 1H, 1i-H), 4.73 (d, $^1J_{C,H} = 168.9$ Hz, 1H, 1g-H), 4.29 (d, $^1J_{C,H} = 154.6$ Hz, 1H, 1d-H). ^{13}C NMR (100 MHz, [D$_6$]acetone): $\delta = 102.6$ (C-1b), 102.0 (C-1d), 101.95 (C-1c), 101.25 (C-1e, C-1f), 101.1 (C-1a), 100.8 (C-1g, C-1h), 100.3 (C-1i). MS (MALDI-TOF): $m/z = 3021$ $[(M+Na)^+]$.

8-(Methoxycarbonyl)octyl 3-*O*-(2-*O*-(2-*O*-(α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-6-*O*-(3,6-di-*O*-(2-*O*-(α-D-mannopyranosyl)-α-D-mannopyranosyl)-α-D-mannopyranosyl)-β-D-mannopyranoside (2): Compound **28** (8.3 mg, 2.7 μmol) and palladium acetate (25 mg, 111 μmol) were stirred in methanol (2.5 mL) under a hydrogen atmosphere for 48 h after which time MALDI-TOF mass spectrometry revealed reaction to be complete. The palladium was separated in a centrifuge and the supernatent decanted. The pellet was resuspended in methanol (2 mL), the phases were again separated in a centrifuge and the supernatent again decanted. This procedure was repeated a further two times. The combined methanol fractions were evaporated under reduced pressure and the residue partitioned between ethyl acetate (0.5 mL) and deuterium oxide (1.5 mL). The aqueous layer was separated and the ethyl acetate layer washed with deuterium oxide (1.5 mL). The combined aqueous layers were lyophilised and the residue purified by atmospheric pressure chromatography on MCI® gel [26] (*CHP20P 75–150 μ; gradient elution: H_2O to MeOH*). The fractions containing the desired material were identified by MALDI-TOF mass spectrometry and the combined fractions were lyophilised. The residue was then further purified by atmospheric pressure chromatography on Sephadex® G10 (eluent: D_2O) to yield the fully deprotected nonasaccharide **2** (1.6 mg, 35%) as a colourless solid. ^{1}H NMR (500 MHz, D_2O): $\delta = $ [5.34 (s, 1H), 5.27 (s, 1H), 5.24 (s, 1H), 5.07 (s, 1H), 4.98 (s, 3H), 4.81 (s, 1H), 4.59 (s, 1H) 9 × anomeric protons], 4.10–3.40 (m, 59H) including 3.63 (s, 3H, CO_2Me), 2.33 (t, $J = 7.5$ Hz, 2H, CH_2CO$_2$Me), 1.59–1.48 (m, 4H) and 1.31–1.19 (m, 8H) (OCH$_2$(CH_2)$_6$CH$_2$CO$_2$Me); MS (MALDI-TOF): $m/z = 1670$ $[(M+Na)^+]$ HRMS (FT-ICR MALDI) calcd for $C_{64}H_{110}O_{48}Na$ $(M+Na^+)$ 1669.6058, found (referenced against an internal bombesin sample) 1669.6125.

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