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Direct Chemical Synthesis of the β-Mannans: Linear and Block Syntheses of the Alternating β-(1→3)-β-(1→4)-Mannan Common to *Rhodotorula glutinis*, *Rhodotorula mucilaginosa*, and *Leptospira biflexa*

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Abstract: Two stereocontrolled syntheses of a methyl glycoside of an alternating β-(1→4)-β-(1→3)-mannohexaose, representative of the mannan from *Rhodotorula glutinis*, *Rhodotorula mucilaginosa*, and *Leptospira biflexa*, are described. Both syntheses employ a combination of 4,6-*O*-benzylidene- and 4,6-*O*-*p*-methoxybenzylidene acetal-protected donors to achieve stereocontrolled formation of the β-mannoside linkage. The first synthesis is a linear one and proceeds with a high degree of stereocontrol throughout and an overall yield of 1.9%. The second synthesis, a block synthesis, makes use of the coupling of two trisaccharides, resulting in a shorter sequence and an overall yield of 4.4%, despite the poor selectivity in the key step.

Introduction

Recently, we described the linear synthesis of two β-mannans,[1] a β-(1→2)-mannooctaose and a β-(1→4)-mannohexaose, employing the 4,6-*O*-benzylidene-directed[2] β-mannosylations developed in our laboratory from either thioglycoside[3] or glycosyl sulfoxide[4] donors, with emphasis on the influence of the linkage type, β-(1→2) or β-(1→4), on stereoselectivity in the growing chain. We describe here the extension of these investigations to the synthesis of an alternating β-(1→3)-β-(1→4)-mannohexaose. This hexasaccharide may be viewed as essentially two repeats, sandwiched between two terminal glycosides, of the basic structural unit of the antigenic mannan, with alternating β-(1→3) and β-(1→4) linkages from *Rhodotorula glutinis*,[5] *Rhodotorula mucilaginosa*,[6] and *Leptospira biflexa*.[7] The particular challenge of this target, aside from the obvious presence of multiple β-mannosidic linkages,[8] is the alternating nature of the chain, necessitating the use of two glycosyl donors with orthogonal protection at positions 3 and 4, which are nevertheless consistent with the requirement for a 4,6-*O*-benzylidene-type protection and nonparticipating groups on O-2 and O-3 in our mannosylation protocols.[3,4] We first describe in full a linear synthesis in which the challenge is met by the judicious combination of benzyl and *p*-methoxybenzyl ethers with benzylidene and *p*-methoxybenzylidene acetals, respectively, in two distinct thioglycosides,[9] and then in a quest for greater efficiency,[10] we present a convergent or block synthesis[11] which eliminates the need for one of these protecting groups, namely, the *p*-methoxybenzyl ether.

Results and Discussion

The linear synthesis of the hexasaccharide began with the preparation of two thioglycosides and their sulfoxides. Thus, phenyl α-D-thiomannopyranoside **1** was converted to benzylidene acetal **2**[12] and the corresponding *p*-methoxybenzylidene acetal **3**[13] in the standard manner. Reaction of **2** with dibutyltin oxide[14] and then *p*-methoxybenzyl chloride and tetrabutylammonium bromide selectively afforded 3-*O*-PMB ether **4**[15] in 94% yield. Reaction with sodium hydride and benzyl bromide then

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(11) (a) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095−1121. (b) Kanie, O. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 407−426.
(12) Oshitari, T.; Shibasaki, M.; Yoshizawa, T.; Tomita, M.; Takao, K.; Kobayashi, S. *Tetrahedron* **1997**, *53*, 10993−11006.
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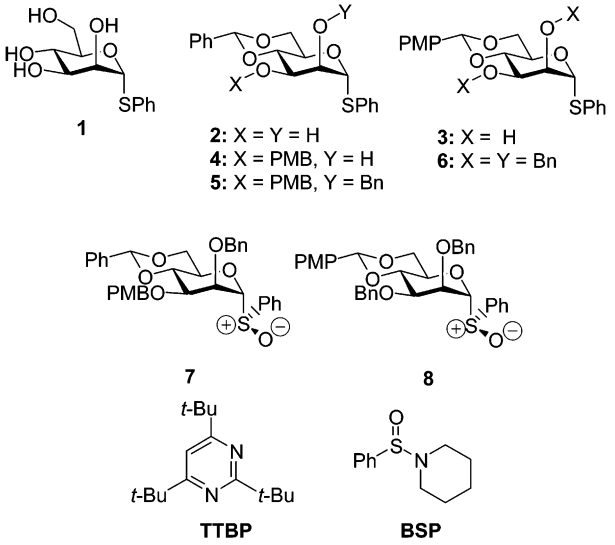
Table 1. Coupling and Selective Deprotection Yields in the Linear Synthesis of **26**

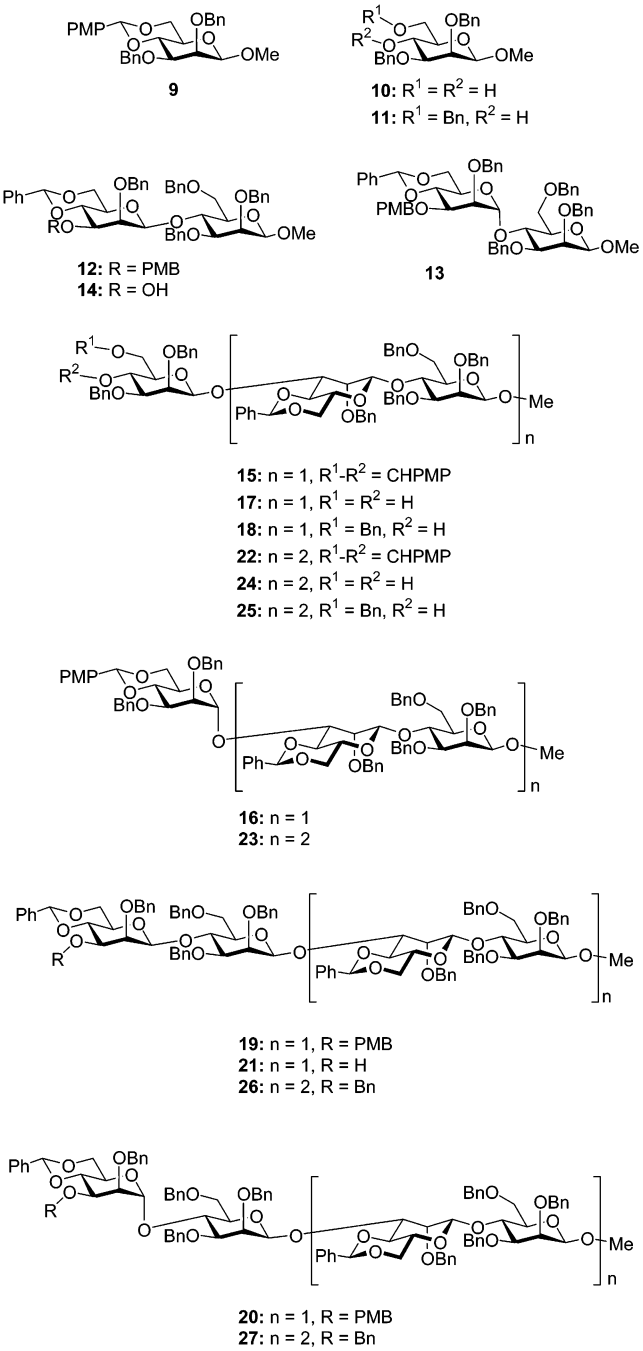
acceptor	donor	linkage	β-glycoside(% yield)	α-glycoside(% yield)	β/α ratio	deprotection (% yield)	benzylation (% yield)
MeOH	**8**		**9** (62)			**10** (97)[a]	**11** (87)
11	**6**	1→4	**12** (81)	**13** (8)	10/1	**14** (83)[b]	
14	**8**	1→3	**15** (72)	**16** (8)	9/1	**17** (70)[a]	**18** (87)
18	**6**	1→4	**19** (62)	**20** (7.5)	7.5/1	**21**(72)[b]	
21	**8**	1→3	**22** (72)	**23** (8)	9/1	**24** (50),[a] (81)[c]	**25** (62)
25	**30**	1→4	**26** (63)	**27** (7)	9/1		

[a] Removal of a PMP acetal with acetic acid. [b] Removal of a PMB ether with DDQ. [c] Yield based on recovered starting material.

provided the fully protected thioglycoside **5** in 90% yield. Benzylation of PMP acetal **3** with sodium hydride and benzyl bromide gave dibenzyl ether **6** in 99% yield. Thioglycosides **5** and **6** were then both transformed to the corresponding sulfoxides **7** and **8**, respectively, in the form of single diastereomers.[16]

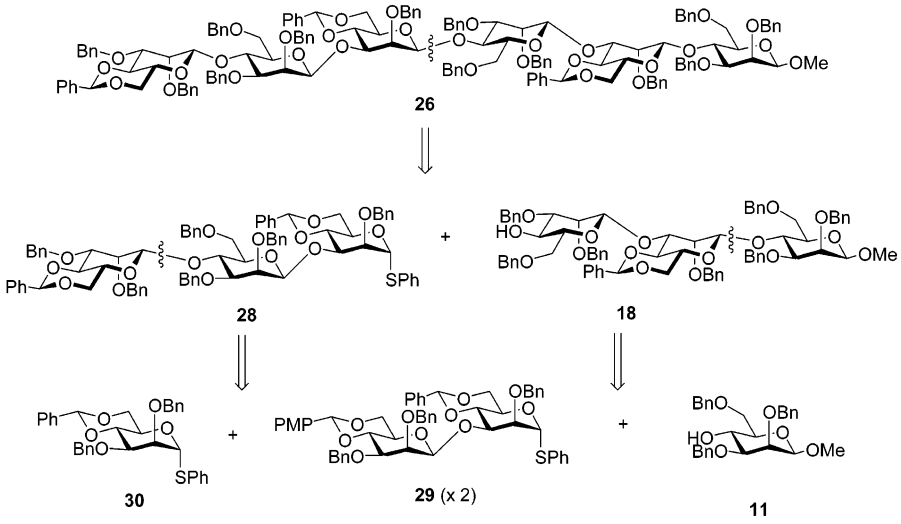


Activation of **8** in dichloromethane at −78 °C with triflic anhydride in the presence of the hindered base TTBP, the standard protocol for sulfoxide β-mannosylation,[4b,17] followed by addition of methanol, gave methyl β-mannoside **9** in 62% yield (Table 1). Glycoside **9** was subsequently obtained directly from thioglycoside **6** by activation with 1-benzenesulfinyl piperidine (BSP) and triflic anhydride in the presence of TTBP in 74% yield. Although the PMP acetal in **9** could potentially be reduced directly to the 6-*O*-PMB ether,[13] leaving the 4-OH free to participate in a coupling with donor **7**, this would have resulted in the need to selectively remove one of two PMB ethers in order for the synthesis to proceed. The preferred protocol was, therefore, the selective removal of the PMB acetal under acidic conditions followed by regioselective 6-*O*-benzylation with dibutyltin oxide and benzyl bromide. Thus, treatment of **9** with glacial acetic acid in dichloromethane gave diol **10** in 97% yield. Reaction with dibutyltin oxide in toluene at reflux, followed by treatment with benzyl bromide and cesium fluoride, provided tri-*O*-benzyl ether **11** in 87% yield (Table 1). Standard coupling of acceptor **11** with donor **7** then provided the β-1,4-linked disaccharide **12** in high yield and selectivity. Treatment of **12** with DDQ cleaved the PMB ether and set the stage for the next coupling reaction, which was achieved with a 9/1 ratio of β/α selectivity by means of donor **8**. Removal of the PMP acetal from the resulting β-trisaccharide **15**, affording diol **17**, required careful monitoring of the reaction progress to avoid concomitant cleavage of the benzylidene acetal. As reported



(16) (a) Crich, D.; Mataka, J.; Sun, S.; Lam, K.-C.; Rheingold, A. R.; Wink, D. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2763−2764. (b) Crich, D.; Mataka, J.; Zakharov, L. N.; Rheingold, A. L.; Wink, D. J. *J. Am. Chem. Soc.* **2002**, *124*, 6028−6036.

Scheme 1. Key Disconnections in the Block Synthesis



by Khorana,[18] this was achieved with acetic acid, but better yields overall were obtained if the reaction was stopped before completion and the unreacted substrate was recovered and resubmitted to the deprotection conditions. Terminal diol **17** was then selectively benzylated on the primary alcohol by the stannylene acetal technology, giving **18** (Table 1). At this stage, each of the five individual steps needed in the iterative sequence toward the hexasaccharide had been successfully demonstrated. Careful repetition of the reaction sequence, with the yields and selectivities indicated in Table 1, eventually led to the fully protected all-β-hexasaccharide **26**. In the course of this synthesis, the β-stereochemistry of **9** and all subsequent β-mannosides were assigned on the basis of the characteristic upfield chemical shift of the H-5 resonance (δ 3.30), an apparent doublet of triplets, which is typical and diagnostic for 4,6-*O*-benzylidene-protected β-mannosides.[4b]

In an attempt to increase efficiency, a convergent approach to **26** was next designed. As set out in Scheme 1, the target was dissected into two trisaccharides, **18** and **28**, each of which could potentially be assembled from a common disaccharide thioglycoside **29**, thereby reducing the overall number of steps significantly.

As envisaged, the block synthesis required two further building blocks, the known 2,3-di-*O*-benzyl-4,6-*O*-benzylidene **30**,[4b] readily obtained by perbenzylation of diol **2**, and the 2-*O*-benzyl derivative **31**. In principle, **31** can be obtained by selective removal of the PMB ether from **5**, but we have preferred to employ a simple biphasic treatment with aqueous tetrabutylammonium hydrogen sulfate and benzyl bromide in dichloromethane,[19] which lead directly to the known[20] monobenzyl ether **31** from diol **2** in 75% yield.[21] Also in the interests of increasing efficiency, this block synthesis has been conducted by the thioglycoside/BSP method[3a] rather than by the sulfoxide method employed in the earlier linear synthesis. Pivotal disaccharide **29** was obtained (Scheme 2) by coupling glycosyl donor **6** to thioglycoside alcohol **31** by the BSP method in 62% yield on a multigram scale; no α-isomer was isolated from this reaction. The success of this enterprise, in which the acceptor itself is a thioglycoside, does not derive from any differential reactivities of **6** and **31**, as in Fraser-Reid's armed/disarmed concept[22] and as employed successfully in the recent one-pot thioglycoside-based oligosaccharide syntheses of the Ley[10a] and Wong[10b] groups. Rather, it is a function of the prior activation of the donor before addition of the acceptor, a standard feature of our β-mannosylation protocols, and from the recognition that 1 mole of the BSP/Tf_2O combination brings about the activation of at least 2 moles of thioglycoside. This latter observation enables the initial activation to be conducted with <50 mol % BSP/Tf_2O, thereby minimizing the amount of thiophilic species in solution when the acceptor is added.[23] The yield of this coupling was further enhanced by the addition of triethyl phosphite after the acceptor was added and before the reaction mixture was allowed to come to room temperature, with the objective, again, being to minimize the possibility of the activation of disaccharide thioglycoside **29** by extraneous thiophiles present in the reaction mixture. The use of phosphites in this manner has previously been successfully demonstrated by van Boom and co-workers in the BSP/Tf_2O and diphenyl sulfoxide/Tf_2O activation of thioglycosides and hemiacetal glycosyl donors.[24−27] The stereochemistry of **29** was assigned in the usual manner on the basis of the chemical shift of the

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(21) We note that this biphasic alkylation is very convenient on a multigram scale with **31** being isolated in high yield by simple recrystallization.

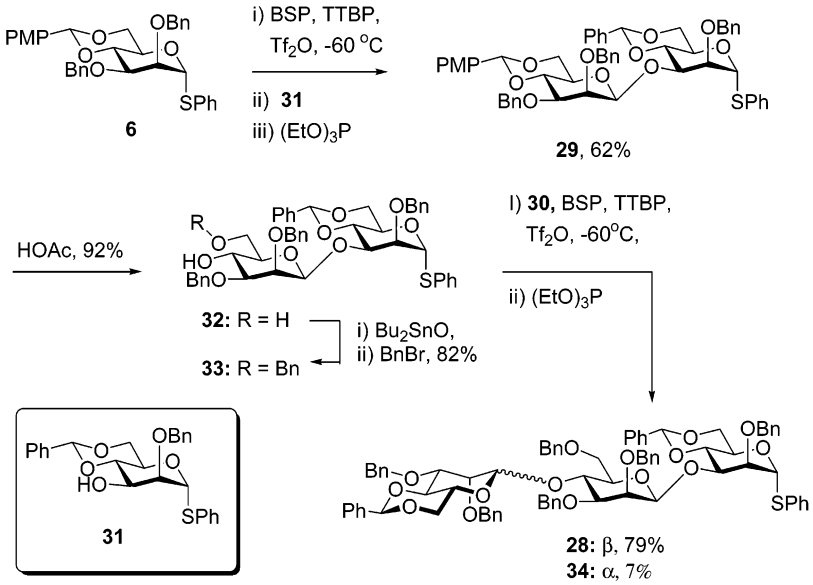
(22) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.

(23) The use of substoichiometric amounts of triflic anhydride in the activation of glycosyl sulfoxides has been similarly noted: (a) ref 2. (b) Yan, L.; Kahne, D. *Synlett* **1995**, 523−524. (c) Gildersleeve, J.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961−5969.

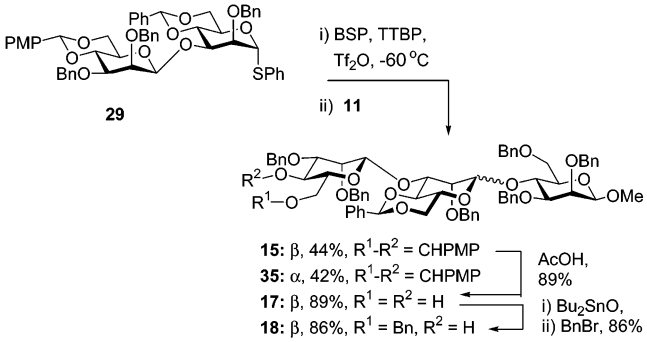
(24) (a) Codée, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519−1522. (b) Codée, J. D. C.; van den Bos, J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947−1950. (c) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057−1064.

(25) For a recent synthesis of a small oligosaccharide library using the thioglycoside/BSP method and involving the use of thioglycoside alcohols as acceptors, see: Yamago, S.; Yamada, H.; Maruyama, T.; Yoshida, J.-i. *Angew. Chem., Int. Ed.* **2004**, *43*, 2145−2148.

Scheme 2. Construction of Tri- and Disaccharide Donors **28** and **29** and of Acceptor **33**



Scheme 3. Synthesis of Trisaccharides **15** and **18**



4,6-*O*-benzylidene-protected β-mannoside H-5 chemical shift at δ 2.97. In addition, **29** displayed two anomeric carbons at δ 98.1 and 85.8 with $^1J_{CH}$ coupling constants of 153.0 and 166.2 Hz, respectively, consistent with the presence of a β-*O*-glycoside[28] and an α-*S*-glycoside.[29] These same methods were used to assign stereochemistry throughout the remainder of the synthesis. Cleavage of the PMP acetal in **29** with acetic acid in the usual manner afforded diol **32**, and this was selectively benzylated on the primary hydroxyl, giving **33**, again, in the standard manner using dibutyltin oxide and benzyl bromide (Scheme 2). Coupling of disaccharide **33** to donor **30**, under the BSP deficient conditions, then completed the synthesis of trisaccharide **28**, which was obtained in 79% yield together with 7% of the α-anomer **34** (β/α = 11/1).

Trisaccharide **15** was readily assembled by coupling donor **29** with the simple acceptor **11** under the standard BSP conditions (Scheme 3). Unfortunately, the selectivity of this particular coupling was poor ($\sim$1/1) and has remained so despite considerable effort directed toward improving it. Nevertheless, trisaccharide **15** could be routinely isolated in 400 mg amounts, sufficient for the completion of the synthesis. In preparation for the final coupling, the PMP acetal of **15** was removed and diol **17** converted to the terminal benzyl ether **18** by the stannylene acetal protocol (Scheme 3).

In the final step of this convergent synthesis, the two trisaccharides, **18** and **28**, were combined by the BSP protocol to give β-hexasaccharide **26** and it's α-anomer **36**, in 35 and 53% yields, respectively, with a β/α ratio of 1/1.5 (Scheme 4). Although the selectivity in this final coupling was, again, disappointing, it is stressed that the coupling was conducted with almost stoichiometric quantities of the two coupling partners (**28**/**18** = 1.38/1) and, despite the poor selectivity, afforded 156 mg of the desired hexasaccharide **26** in a single reaction. The spectral data of hexasaccharide **26**, obtained by the convergent block synthesis, matched those from the sample obtained by the linear route exactly, thereby substantiating the methods of stereochemical assignment used in both syntheses. Finally, hydrogenolysis of **26** over palladium on carbon afforded the target, alternating mannan **37** in 93% isolated yield.[30] This mannan displayed three distinct sets of anomeric resonances in the ^{1}H and ^{13}C NMR spectra (D_2O), consistent with the two β-(1$\rightarrow$3)- and three β-(1$\rightarrow$4)-linkages and the terminal β-methyl mannoside. Impor-

(26) The use of phosphites to clean up extraneous thiophiles in sulfoxide glycosylations has also been described by van Boom and others: (a) Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015−4018. (b) Alonso, I.; Khiar, N.; Martin-Lomas, M. *Tetrahedron Lett.* **1996**, *37*, 1477−1480.

(27) Other traps for thiophilic agents previously employed in the sulfoxide method include alkenes and alkynes: (a) ref 17b. (b) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580−1581.

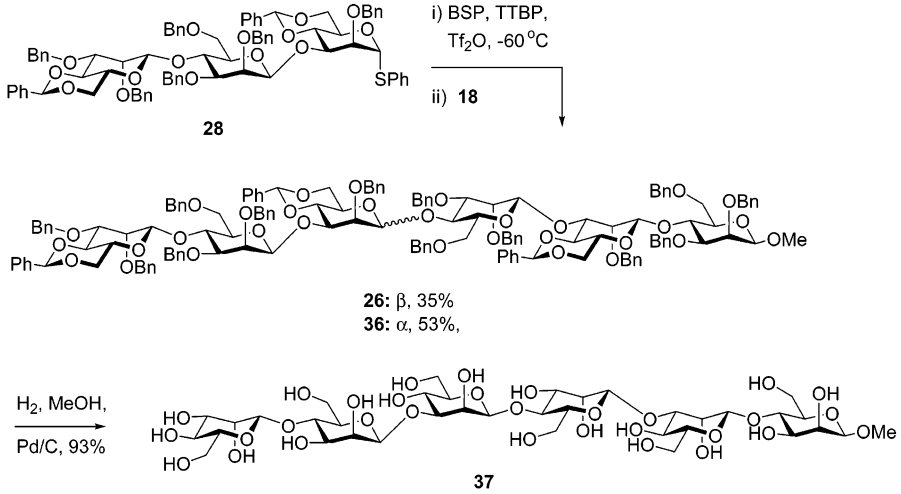
(28) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293−297.

(29) Crich, D.; Li, H. *J. Org. Chem.* **2000**, *65*, 801−805.

(30) Needless to say, the identical substance was obtained on hydrogenolysis of **26** derived from either the linear or the convergent routes.

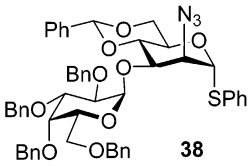
(31) (a) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263−2266. (b) Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787−1789. (c) Dudkin, V. Y.; Miller, J. S.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 1791−1793. (d) Kim, K. S.; Kang, S. S.; Seo, Y. S.; Kim, H. J.; Jeong, K.-S. *Synlett* **2003**, 1311−1314. (e) Crich, D.; de la Mora, M. A.; Cruz, R. *Tetrahedron* **2002**, *58*, 35−44. (f) Crich, D.; Dai, Z. *Tetrahedron* **1999**, *55*, 1569−1580. (g) Nicolaou, K. C.; Mitchell, H. J.; Rodriguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Conley, S. R. *Chem.—Eur. J.* **2000**, *6*, 3149−3165. (h) Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640−4646. (i) Dudkin, V. K.; Miller, J. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 736−738. (j) Mandal, M.; Dudkin, V. Y.; Geng, X.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2557−2561. (k) Wu, X.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 1853−1857. (l) Mong, T. K.-K.; Lee, H. K.; Durón, S. G.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 797−802. (m) Yun, M.; Shin, Y.; Chun, K. H.; Jen, S. *Bull. Korean Chem. Soc.* **2000**, *21*, 562−566. (n) Weingart, R.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753−8758. (o) Tsuda, T.; Sato, S.; Nakamura, S.; Hashimoto, S. *Heterocycles* **2003**, *59*, 509−515. (p) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477−8481. (q) Litjens, R. E. J. N.; Leeuwenburgh, M. A.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8693−8696. (r) Durón, S. G.; Polat, T.; Wong, C.-H. *Org. Lett.* **2004**, *6*, 839−841.

Scheme 4. Block Synthesis of the Hexasaccharide **26** and Completion of the Synthesis



tantly, all of the anomeric carbon resonances had $^1J_{CH}$ coupling constants in the region of 157−162 Hz and serve, therefore, as a final vindication of the stereochemical assignment.

The poor selectivity in the couplings of disaccharide donor **29** with acceptor **11** (Scheme 3) and of trisaccharide donor **28** with acceptor **18** (Scheme 4) is striking and stands in marked contrast to the several successful highly stereoselective couplings reported in the literature using our 4,6-*O*-benzylidene-protected β-mannosyl donors or subsequent derivations.[9,24c,31] However, such poor selectivity is not entirely without precedent as we have previously noted that 2-*O*-benzyl-4,6-*O*-benzylidene mannosyl donors carrying a bulky silyl ether on O-3 gave poor selectivity in coupling reactions.[32,33] The problem, a clear limitation of our method, obviously lies with donors carrying bulky groups on O-3. As before,[32] we can only suggest that bulky groups on O-3, whether protecting groups or glycosidic units, suffer from compression between the benzylidene ring and the benzyl ether on O-2. This results in a situation in which the O-2 benzyl group populates a conformation in which it is located above the anomeric carbon, thereby hindering nucleophilic attack on the β-face and resulting in significantly reduced selectivity. This rationale is bolstered by the recent observation of high β-selectivity in the coupling reactions of donor **38**, following activation with diphenyl sulfoxide and triflic anhydride.[24a,c] Whatever the eventual reason, the obvious conclusion is that future block syntheses should be designed so as to avoid mannosyl donors carrying oligosaccharide chains on O-3.



It is appropriate to compare the two syntheses of the protected hexasaccharides presented here. As the initial steps and donor preparations are largely common to both syntheses, the linear synthesis begins with acceptor **11** and the block synthesis with acceptor **31**, both of which are coupled to donor **6** (Table 1 and Scheme 1). Thus, starting from **11**, we observe that the linear sequence proceeds in 11 steps and 1.9% overall yield to hexasaccharide **26** (Table 1). The block synthesis, on the other hand, progresses from **31** to **26**, with a longest linear sequence of 8 steps and an overall yield of 4.4%, despite the modest yields associated with the lack of stereoselectivity in the final two couplings (Schemes 2−4). In oligosaccharide synthesis, as in the total synthesis of other classes of molecules, the arithmetic demon is best outwitted by well-designed, convergent routes.

It is of some interest that the ^{13}C and ^1H NMR spectra of hexasaccharide **37** (recorded in D_2O at 65 °C) closely mimic those of the naturally occurring β-(1→3)-β-(1→4)-mannan (recorded in D_2O at 70 °C[5b] and 65 °C[7,34]). Thus, in the natural mannan, two anomeric carbon resonances are observed at δ 98.7[5b] (97.5,[6] 98.7[7]) and δ 101.6[5b] (100.9,[6] 101.7[7]). Likewise, the natural mannan has two anomeric protons signals at δ 4.85[6] (4.85[7]) and 4.73[6] (4.72[7]), consistent with a highly regular structure of alternating (1→3) and (1→4) linkages. Synthetic mannan **37** has a pair of superimposed anomeric carbon signals at δ 99.9, representing the two β-(1→3)-linkages, a second unresolved pair at δ 102.9 together with a closely allied third resonance at δ 103.1, indicative of the two internal and the one terminal β-(1→4) anomeric bonds, and a final signal at δ 103.9, belonging to the β-methyl glycoside. In the proton spectrum, **37** has two overlapping anomeric resonances at δ 4.86, a group of three unresolved signals at δ 4.73, and an isolated resonance at δ 4.59. Again, this is consistent with the presence of two β-(1→3)-linkages, three β-(1→4) anomeric bonds, and the terminal methyl glycoside (δ 4.59). It is evident from the grouping of the anomeric signals in both the ^{13}C and the ^1H NMR spectra and the parallels with the spectra of the natural mannan that hexasaccharide **37** already shows the beginnings of an organized, regular structure. This is to be contrasted with the irregular structure of the collapsed helical β-(1→2)-mannooctaose and the highly regular structure of the β-(1→4)-mannohexaose, whose syntheses we have also completed.[1] In agreement with these observations, hexasaccharide **37**, a white microcrystalline solid, has a melting point of 168−170 °C,

(32) Crich, D.; Dudkin, V. *Tetrahedron Lett.* **2000**, *41*, 5643−5646.
(33) This is to be contrasted with the 3-*O*-carboxylate-protected mannosyl donors and the 2,3-*O*-carbonate-protected mannosyl donors, both with 4,6-*O*-benzylidene acetals, which are extremely α-selective for a different set of reasons: (a) ref 31h. (b) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291−1297. (c) Crich, D.; Vinod, A. U.; Picione, J. *J. Org. Chem.* **2003**, *68*, 8453−8458.
(34) The temperature at which the NMR spectra in ref 6 were measured was not recorded.

which, fittingly, sits between the melting points of >300 °C that were recorded for the β-(1→4)-mannohexaose and the gummy, noncrystalline nature of the β-(1→2)-mannooctaose.

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Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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