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Direct Chemical Synthesis of the β-D-Mannans: The β-(1→2) and β-(1→4) Series

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Abstract: The direct syntheses of a β-(1→2)-mannooctaose and of a β-(1→4)-mannohexaose are reported by means of 4,6-*O*-benzylidene-protected β-mannosyl donors. The synthesis of the (1→2)-mannan was achieved by means of the sulfoxide coupling protocol, whereas the (1→4)-mannan was prepared using the analogous thioglycoside/sulfinamide methodology. In the synthesis of the (1→4)-mannan, the glycosylation yields and stereoselectivities remain approximately constant with increasing chain length, whereas those for the (1→2)-mannan consist of two groups with the formation of the tetra- and higher saccharides giving yields and selectivities consistently lower than those of the lower homologues. The decrease in yield after the trisaccharide in the (1→2)-mannan synthesis is attributed to steric interference by the n-3 residue and is consistent with the collapsed, disordered structure predicted by early computational work. The consistently high yields and selectivities seen in the synthesis of the (1→4)-mannan are congruent with the more open, ordered structure originally predicted for this polymer. The lack of order in the structure of the (1→2)-mannan, as compared to the high degree of order in the (1→4)-mannan, is also evident from a comparison of the NMR spectra of the two polymers and even from their physical nature: the (1→2)-mannan is a gum and the (1→4)-mannan is a high melting solid.

Introduction

The β-mannans are a group of homopolymers of D-mannopyranose featuring the 1,2-*cis*-equatorial glycosidic bond. The structure and function of these oligosaccharides depend heavily on the linkage isomer. The β-(1→4)-mannan is a primary constituent of alimentary gums and of hard and soft woods according to the type and degree of glycosylation.[1] The galactomannans, β-(1→4)-mannans decorated at the 6-position with varying amounts of α-galactopyranosides, are major components of guar and other gums used in the food and pharmaceutical industries.[2] The glucomannans, linear copolymers of β-(1→4)-linked mannose with β-glucopyranoside, make up 3−5% of the dry weight of most hardwoods, whereas partially acetylated glucomannans and galactoglucomannans (6-*O*-galactosylated glucomannans) are found in soft woods.[3] The β-(1→2)-mannans, on the other hand, are critical components of the *Candida albicans* cell wall phosphopeptidomannan. The *C. albicans* β-(1→2)-mannans are immunogenic and elicit specific antibodies in both humans and animals.[4] Antibodies raised against β-(1→2)-oligomannosides have been shown to be protective against *C. albicans* in rodent models of systemic and vaginal candidosis.[5] It has been shown that β-(1→2)-mannosides derived from *C. albicans* phosphopeptidomannans induce TNF[1]-α synthesis from cells of the macrophage lineage and bind to macrophage cell membranes.[6] Furthermore, an antigenic phospholipomannan has been isolated, purified, and shown to be a strong TNF-α inducer in vivo and in vitro.[7] In addition to their role in candidosis, β-(1→2)-mannans have been demonstrated to be components of the yeast cell wall mannan of *Torulaspora delbrueckii*.[8] An intriguing β-mannan in which (1→3) and (1→4) linkages alternate is a major part of the antigenic oligosaccharides from *Leptospira biflexa*.[9]

Any chemical synthesis of the β-mannans designed to provide them as predetermined homogeneous samples, as opposed to

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the heterogeneous natural isolates, must confront the issue of the stereoselective synthesis of the challenging β-mannosidic bond.[10] In fact, the β-mannans might be seen as the ultimate proving ground for any technology aspiring to the synthesis of β-mannosides. Indeed, the challenge of the β-(1→2)-mannans has been met by two groups, both using indirect methods. Thus, Bundle and Nitz first synthesized the β-(1→2)-linked mannotetraose,[11] then the corresponding hexaose,[12] employing the Lichtenthaler strategy of silver salt-mediated stereoselective β-mannosylation with a 2-ulosyl bromide donor,[13] thereby allowing them to determine the solution structure of these fascinating oligomers.[14] Fraser-Reid and co-workers, more recently, completed a synthesis of the β-(1→2)-linked mannooctaose, employing a strategy of stereoselective β-glucosylation, selective deprotection, and inversion by a two-step oxidation−reduction protocol.[15] The β-(1→4)-linked mannotriose has been synthesized by Nikolaev and co-workers, again, by an indirect route involving the gluco- to manno-inversion, by a two-step triflation−displacement sequence, following glycosylation.[16] In this paper, we present our direct syntheses of a β-(1→2)-mannooctaose[17] and a β-(1→4)-mannohexaose, applying a stereoselective β-mannosylation sequence developed in this laboratory.[18]

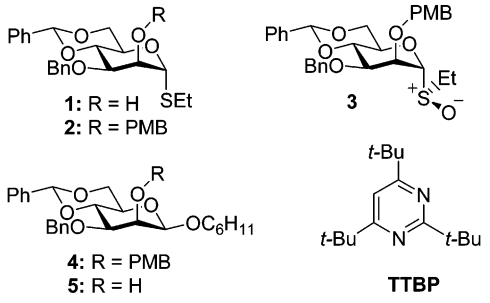
Results and Discussion

The synthesis of the β-(1→2)-linked mannooctaose began with the known thioglycoside **1**, which was converted to the corresponding 2-*O*-*p*-methoxybenzyl ether **2** and then to sulfoxide **3**. This compound was obtained as a single stereoisomer at sulfur, consistent with the precedent in the α-series,[19] and was assigned the $(R)_S$ configuration by analogy with that of crystallographically determined structures.[20] Donor **3** was coupled to cyclohexanol, arbitrarily chosen as a capping group for the reducing end of the octaose, by the standard protocol involving prior activation[18,21] of the sulfoxide in dichloromethane at low temperature with trifluoromethanesulfonic anhydride in the presence of the hindered base, 2,4,6-tri-*tert*-butylpyrimidine (TTBP).[22] This protocol results in the rapid, clean formation of an α-mannosyl triflate,[23] which is the true glycosyl donor in an S_N2-like process possibly involving a transient contact ion pair. Cyclohexyl mannoside **4** was obtained with high yield and selectivity (Table 1), and the β-stereochemistry was assigned on the basis of the unusual, somewhat upfield, H-5 chemical shift of δ 3.33, which is diagnostic of the β-stereochemistry in the 4,6-*O*-benzylidene-protected mannosides.[18b] The anomeric stereochemistry in all subsequent coupling products was similarly assigned on the basis of the number of upfield H-5 resonances, which were always one less in the minor α-product compared to the major β-isomer. Removal of the PMB group with DDQ then provided alcohol **5**, thereby completing the first cycle of the two-step iterative sequence. Repeated iteration of this protocol, with the yields and selectivities reported in Table 1, ultimately provided the protected mannooctaose **26** with the all β-configuration.

Table 1. β-(1→2) Linkage Yields and Selectivities in the Synthesis of **28**

acceptor	β-glycoside (% yield)	α-glycoside (% yield)	β/α ratio	freed alcohols (% yield)
$C_6H_{11}OH$	**4** (77)	− (0)	β only	**5** (85)
5	**6** (94)	− (0)	β only	**7** (97)
7	**8** (89)	**9** (9)	9.9/1	**10** (91)
10	**11** (77)	**12** (20)	3.9/1	**13** (85)
13	**14** (69)	**15** (16)	4.3/1	**16** (80)
16	**17** (68)	**18** (15)	4.5/1	**19** (85)
19	**20** (64)[a]	**21** (13)[a]	4.9/1	**22** (67), **23** (14)
22	**24** (64)[a]	**25** (14)[a]	4.5/1	**26** (71), **27** (13)

[a] Anomeric pairs **20** and **21**, and **24** and **25**, isolated in 77 and 78% yields, respectively, could not be separated chromatographically. The ratios given were therefore determined after removal of the PMB groups when separation was possible.



Inspection of Table 1 reveals that yields and selectivities in the coupling reaction decreased dramatically after the formation of trisaccharide **8**. In other words, the glycosylation of trisaccharide alcohol **10**, and all subsequent homologues, was less selective than that of cyclohexanol, monosaccharide **5**, and disaccharide **7**. Despite the dramatic decrease in selectivity between alcohols **7** and **10**, the selectivities and yields of subsequent couplings are all clustered in a similar range. The implication is that there is a structural change between alcohol **7** and its homologue **10**, which impacts the chemistry in a deleterious manner. Fortuitously, alcohol **13** was obtained as crystals suitable for X-ray diffraction; analysis of the ensuing

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(19) Crich, D.; Sun, S.; Brunckova, J. *J. Org. Chem.* **1996**, *61*, 605−615.
(20) This selectivity is a direct result of the exo-anomeric effect, which in the α-series, exposes one sulfur lone pair to solvent thereby predisposing it to oxidation but shields the second underneath the pyranose ring: (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.
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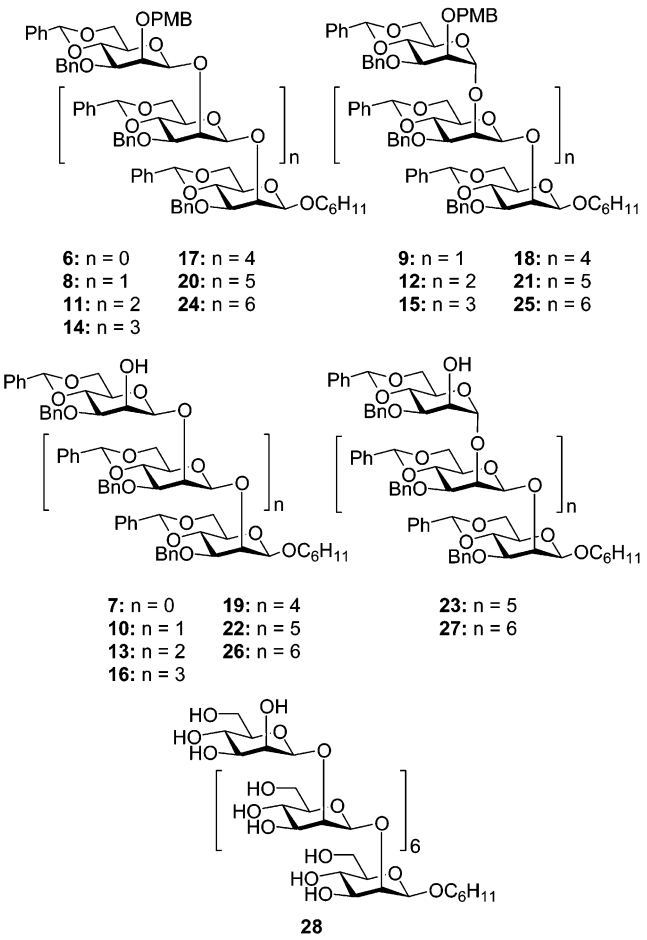
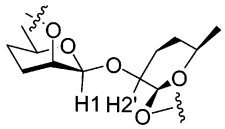


structure confirmed the all β-structure, initially assigned spectroscopically on the basis of the H-5 chemical shifts, and revealed **13** to adopt a somewhat disordered, collapsed helical structure in which the fourth pyranose ring is situated approximately above the first.[24] In terms of reactivity, this means that the introduction of the forth residue (i.e., the formation of **11**) and of all subsequent residues is subject to additional steric constraints arising from the proximity of the fully protected n-3 pyranose ring. The irregular nature of the collapsed helical structure, evident from the glycosidic torsion angles in Table 2, presumably continues as the chain grows and is responsible for the minor fluctuations in yield and selectivity apparent in subsequent couplings.

The decrease in yield and selectivity at the level of formation of the tetrasaccharide is not unique to the synthesis presented here. At the outset of our work on **28**, Bundle and Nitz reported a synthesis of an analogous tetrasaccharide,[11] which was subsequently taken through two further iterations of their sequence to the hexasaccharide,[12] when similar problems became apparent.[25] In a later synthesis of an analogous mannooctaose by Fraser-Reid and co-workers, coupling yields remained largely constant throughout the complete sequence, but it was specified that generous excesses of donor were employed in order to achieve the high yields.[26] This contrasts with the synthesis described here in which the donor was never employed in greater than a 2-fold excess.

Table 2. Glycosidic Bond Torsion Angles in Tetrasaccharide **13**[a]



	Cyc–a	a–b	b–c	c–d
φ (H1−C1−O−C2′)	43.7	44.4	18.3	31.3
ψ (C1−O−C2′−H2′)	−15.3	10.7	−8.7	13.6

[a] Where a and d are the sugars at the reducing and nonreducing ends of the chain, respectively.

Table 3. β-(1→4) Linkage Yields and Selectivities in the Synthesis of **56**

acceptor	β-glycoside (% yield)	α-glycoside (% yield)	α/β ratio	deprotection (% yield)	esterification (% yield)
MeOH	**30** (82)	**31** (8)	1/10	**35** (89)	**36** (98)
36	**37** (80)	**38** (9)	1/9	**39** (85)	**40** (88)
40	**41** (77)	**42** (8)	1/9	**43** (85)	**44** (88)
44	**45** (72)	**46** (8)	1/9	**47** (87)	**48** (89)
48	**49** (71)	**50** (8)	1/9	**51** (88)	**52** (86)
52	**53** (73)	**54** (7)	1/10		

Finally, hydrogenolysis of **26** over palladium charcoal cleanly afforded mannooctaose **28** in high yield, whose NMR spectra reveal the presence of eight distinct glycosidic linkages, consistent with the persistence of the disordered structure in aqueous solution.

In principle, the synthesis of the β-(1→4)-mannan, like that of β-(1→2)-mannan **28**, may be achieved by iteration of a two-step protocol involving 4,6-*O*-benzylidene-mediated β-mannosylation followed by unmasking of the 4-OH group at the reducing end of the chain by regioselective reductive cleavage of the benzylidene acetal. This latter operation is typically wrought with sodium cyanoborohydride and hydrogen chloride in dry ether,[27] although more recent reagent combinations are also available for the same task.[28] In the synthesis of the β-(1→4)-mannan, preference was also given to the activation of a thioglycoside donor with the combination of 1-benzenesulfonyl piperidine (BSP)[18c] and triflic anhydride over the triflic anhydride-mediated sulfoxide coupling used in the chronologically earlier synthesis of β-(1→2)-mannan **28**. With these considerations in mind, activation of thioglycoside **29** with BSP and Tf_2O in the presence of TTBP, followed by the addition of methanol, gave the methyl glycoside **30** in 82% yield along with 8% of the α-anomer **31** in excellent agreement with similar couplings to methanol conducted by the sulfoxide method (Table 3). Reduction of **30** with sodium cyanoborohydride and hydrogen chloride in ether proceeded according to plan and afforded 6-*O*-benzyl-4-hydroxy sugar **32** in 72% yield. When this alcohol was coupled to donor **29** with BSP and Tf_2O in the usual manner, β-disaccharide **33** was obtained in 73% yield together with 7% of the α-anomer **34**. Unfortunately, when the cyanoborohydride−hydrogen chloride protocol was applied to the regioselective cleavage of the benzylidene acetal in **34**, very

(24) Details of the crystal structure may be found in the Supporting Information for the original communication (ref 17).
(25) In the Bundle and Nitz synthesis, the reported yields for the formations of the β-di-, tri-, tetra-, penta-, and hexasaccharides were 78, 60−65, 48, 51, and 48%, respectively, with the reactions typically conducted with an approximately 4-fold excess of glycosyl donor (refs 11 and 12).
(26) The coupling yields reported are all in the range of 83−92%, with the specification of 7 equiv of donor in an experimental footnote (ref 15).
(27) (a) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97−101. (b) Garegg, P. J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1993; pp 53−67.
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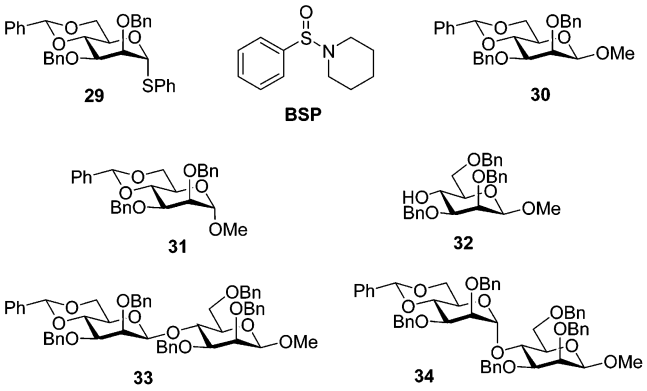
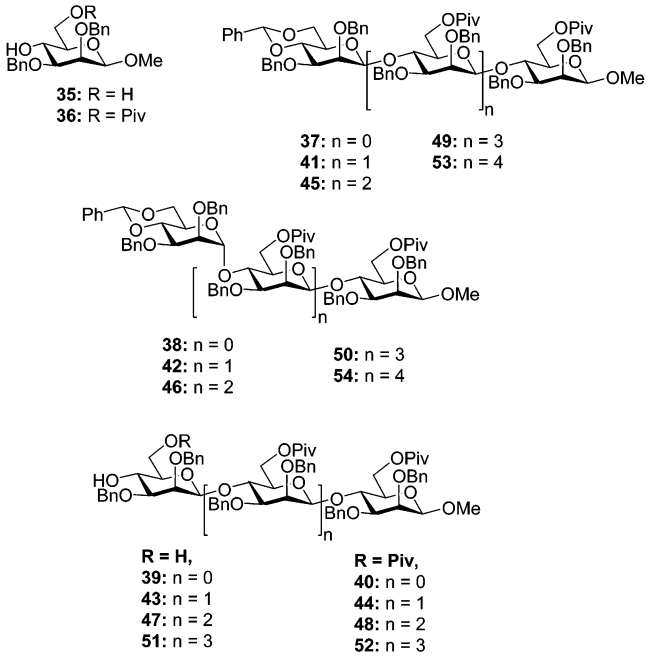
large excesses of both reagents, coupled with long reaction times, were required to bring about the complete conversion of **34**. Not too surprisingly, the long reaction times and excess of strong acid employed for this conversion ensured that the formation of the desired product was marred by the onset of decomposition. The increased requirement for acid and long reaction times in the reduction of **34** is presumably linked to the presence of 10 ether oxygens of similar basicity, as opposed to the 6 in monosaccharide **30**, which significantly reduces the overall level of protonation at the acetal required for reduction.[29]



Reasoning that this problem could only get worse as the synthesis advanced, we turned to an alternative sequence involving complete removal of the benzylidene group followed by selective reprotection of the primary 6-OH group. Although this necessitated the addition of an extra step in each repetition of the cycle, it did provide us with the opportunity to examine the effect of a sterically bulky O-6 protecting group in the glycosyl acceptor.

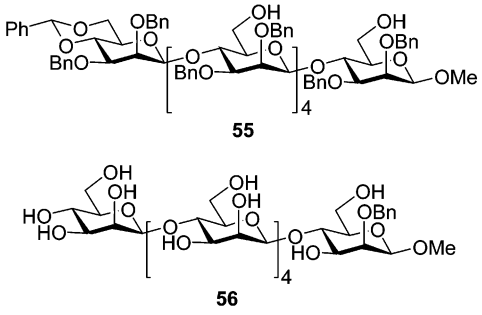
Accordingly, treatment of methyl glycoside **30** with neopentyl glycol and camphorsulfonic acid in dichloromethane afforded diol **35** in 89% yield. This was then converted to monopivalate **36** in 98% yield with pivaloyl chloride, DMAP, and triethylamine in dichloromethane. Coupling of **36** to donor **29** under the standard BSP conditions afforded disaccharide **37** and it's α-anomer **38** in 80 and 9% yield, respectively, thereby demonstrating the coupling reaction to be unaffected by the bulky ester protecting O-6 of the acceptor. Removal of the benzylidene acetal from **37** and selective introduction of the pivalate group, ultimately giving **40**, proceeded uneventfully (Table 3), thereby validating the three-step iterative protocol. The synthesis of hexasaccharide **53** was completed accordingly, with the yields and selectivities for each iteration set out in Table 3. In the synthesis of **53**, stereochemical assignment of the newly formed glycosidic bond in each cycle was greatly facilitated by the presence of only a single benzylidene group, unlike the synthesis of **28** wherein each step introduced a further benzylidene acetal. Thus, at each stage, the β-glycoside clearly exhibited a single mannose H-5 in the region δ 3.1−3.3, whereas the corresponding α-anomer had no resonance in this region. In the absence of confirmatory crystal structures, we also determined the $^1J_{CH}$ coupling constants for the α- and β-anomers at each stage and found them to be in full agreement with the assigned structures.

(29) Note that the standard protocol for this cleavage already requires a considerable excess of HCl, even for a monosaccharide (ref 28).



Inspection of the yields and anomeric selectivities in Table 3 shows that there is no significant decrease as the chain length grows, which is in stark contrast to the synthesis of β-(1→2)-mannan **28** (Table 1). This difference is in full accord with the extended ribbonlike structure anticipated[30] for β-(1→4)-mannans as opposed to the collapsed helical structure of the β-(1→2)-mannan.[30]

Deprotection of hexasaccharide **53** was achieved by saponification with sodium methoxide in hot methanol, affording pentanol **55** in 94% yield. The synthesis was completed by hydrogenolysis over palladium charcoal, which provided pure **56** in 87% yield.



With the two mannans, **28** and **56**, in hand, it is instructive to compare their physical properties. In the ^{1}H NMR spectrum of **28**, seven distinct anomeric hydrogen resonances are clearly visible at 500 MHz, while the ^{13}C spectrum at 125 MHz shows eight separate anomeric carbon signals. The ability to distinguish almost the complete set of anomeric proton and carbon resonances in this manner is in full accord with the irregular helical structure predicted in 1971[30] for this β-(1→2)-mannan, with the structure proposed for the corresponding hexasaccharide by Bundle based on NOE measurements[14] and with the X-ray structure of the protected tetrasaccharide **13**. In stark contrast,

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hexasaccharide **56**, with the predicted[30] more open, ordered structure of the β-(1→4)-mannan, has very simple ^{1}H and ^{13}C spectra resulting from extensive congruence between the various residues in the chain. Remarkably, the ^{13}C NMR spectrum of **56**, recorded at 125 MHz, shows only two anomeric carbon resonances in a 5:1 ratio. The ^{1}H NMR spectrum has four anomeric signals grouped into one resonance and two other individual ones. Finally, the contrast between the disordered **28** and the highly ordered **56** is also reflected in the physical state of the two compounds; simple evaporation of water from a solution of **56** provides the mannohexaose as a white, microcrystalline solid, with mp >300 °C, whereas 2 years of efforts have so far failed to induce the gummy **28** to form crystals. Efforts continue to obtain crystals of both mannans suitable for X-ray analysis.

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

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