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Synthesis of the *C*-Linked Disaccharide α-D-Man-(1→4)-D-Man Employing a SmI_2-Mediated *C*-Glycosylation Step: En Route to Cyclic *C*-Oligosaccharides

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Received September 4, 2002

Investigations are reported on the assembly of the *C*-linked disaccharide α-D-Man-(1→4)-D-Man, representing the first steps in our projected synthesis of a cyclic *C*-oligomer containing repeating units of this *C*-dimer. The key step in this synthesis uses a SmI_2-mediated coupling of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl 2′-pyridyl sulfone with a C4-formyl branched mannopyranoside unit, affording the *C*-disaccharide derivative with complete stereocontrol at the two new stereogenic centers. Subsequently, a modified tin hydride based deoxygenation produced the target carbohydrate analogue. The synthesis of the C4-formyl monosaccharide makes use of a stereoselective radical-based allylation followed by double bond migration and ozonolysis.

Introduction

α-, *β*-, and *γ*-cyclodextrins are macrocyclic oligomers containing six, seven, and eight α-(1→4)-glucopyranose units, respectively, which are prepared by the enzymatic degradation of amylose. These compounds have occupied a long-standing interest among chemists in industry and academia because of their rigid and hydrophobic cavities, which permits formation of inclusion complexes with numerous low-weight molecular compounds.[1] The applications of such cyclic oligosaccharides are vast and range from their use to increase stability and/or solubility of pharmaceuticals to starting materials for the design of artificial enzymes and molecular machines. Structurally modified cyclodextrins with increased stability or selectivity are therefore constantly being sought. Such modifications are commonly achieved by chemically altering the cyclodextrins or by de novo synthesis with monosaccharide units other than glucose.[2,3] Another way of increasing chemical stability, as well as altering the hydrophobicity of the cavity, is to replace the interglycosidic linkages with methylene groups.[4−6] We[7] and others[8,9] have previously demonstrated that *C*-glycosylations involving anomeric Sm(III) species are excellent means for obtaining *C*-disaccharides and higher oligomers thereof employing intact monosaccharide units in a synthetic approach that lies close to those of the well-

(1) A whole issue of *Chemical Reviews* (*Chem. Rev.* **1998**, *98*, issue 5) has been devoted to the chemistry and applications of cyclodextrins.

(2) Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977.

(3) Gattuso, G.; Nepogodiev, S. A.; Stoddart, J. F *Chem. Rev.* **1998**, *98*, 1919.

(4) (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, FL, 1995. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Exeter, UK, 1995. (c) Vogel, P.; Ferritto, R.; Kraehenbuehl, K.; Baudat, A. *Carbohydrate Mimics, Concept and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1997; Chapter 2, p 19. (d) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913. (e) Beau, J.-M.; Vauzeilles, B.; Skrydstrup, T. *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Heidelberg, Germany, 2001; Vol. 3, p 2679. (f) Skrydstrup, T.; Vauzeilles, B.; Beau, J.-M. *Oligosaccharides in Chemistry and Biology—A Compresensive Handbook*; Ernst, B., Sinaÿ, P., Hart, G., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, p 495.

(5) For recent examples of *C*-disaccharide synthesis, see: (a) Liu, L.; Postema, M. H. D. *J. Am. Chem. Soc.* **2001**, *123*, 8602. (b) Vauzeilles, B.; Sinaÿ, P. *Tetrahedron. Lett.* **2001**, *42*, 7269. (c) Jiménez-Barbero, J.; Demange, R.; Schenk, K.; Vogel, P. *J. Org. Chem.* **2001**, *66*, 5132. (d) Postema, M. H. D.; Calimente, D.; Liu, L.; Gehrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061. (e) Pasquarello, C.; Picasso, S.; Demange, R.; Malissard, M.; Berger, E. G.; Vogel, P. *J. Org. Chem.* **2000**, *65*, 4251. (f) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 2939. (g) Khan, N.; Cheng, X.; Mootoo, D. *J. Am. Chem. Soc.* **1999**, *121*, 4918.

(6) For the synthesis of higher *C*-oligomers, see: (a) Haneda, T.; Goekjian, P. G.; Kim, S. H.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 490. (b) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160. (c) Sunderlin, D. P.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 9802. (d) Sunderlin, D. P.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5267. (e) Dondoni, A.; Kleban, M.; Zuurmond, H.; Marra, A. *Tetrahedron Lett.* **1998**, *39*, 7991. (f) Xin, Y.-C.; Zhang, Y.-M.; Mallet, J.-M.; Glaudemans, C. P. J.; Sinaÿ, P. *Eur. J. Org. Chem.* **1999**, 471. (g) Dondoni, A.; Mizuno, M.; Marra, A. *Tetrahedron Lett.* **2000**, *41*, 6657. (h) Dondoni, A.; Marra, A.; Mizuno, M.; Giovannini, P. P. *J. Org. Chem.* **2002**, *67*, 4186.

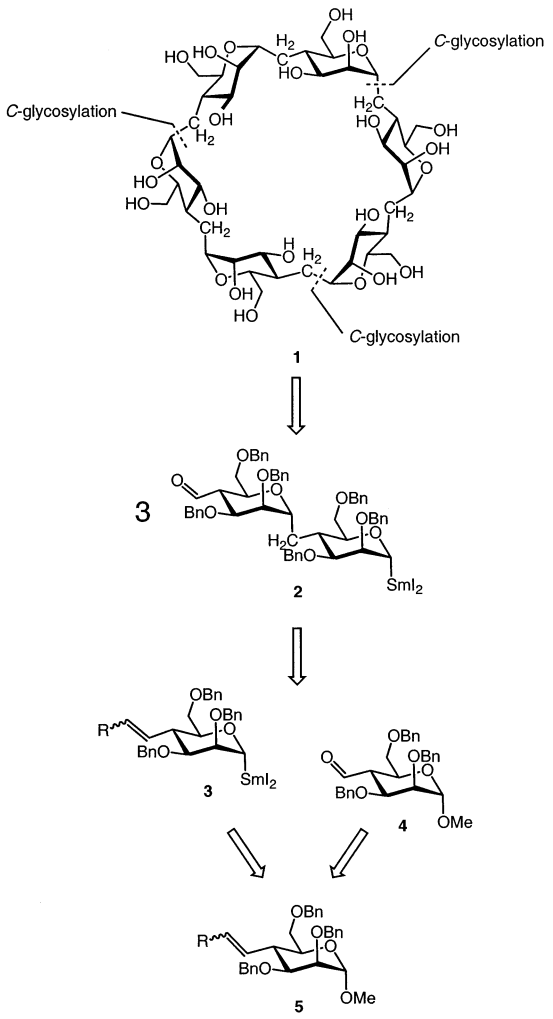
(7) (a) Mazéas, D.; Skrydstrup, T.; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 909. (b) Jarreton, O.; Skrydstrup, T.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1996**, 1661. (c) Urban, D.; Skrydstrup, T.; Riche, C.; Chiaroni, A.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1996**, 1883. (d) Jarreton, O.; Skrydstrup, T.; Beau, J.-M. *Tetrahedron Lett.* **1997**, *36*, 303. (e) Skrydstrup, T.; Jarreton, O.; Mazéas, D.; Urban, D.; Beau, J.-M. *Chem. Eur. J.* **1998**, *4*, 655. (f) Urban, D.; Skrydstrup, T.; Beau, J.-M. *J. Org. Chem.* **1998**, *63*, 2507. (g) Urban, D.; Skrydstrup, T.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1998**, 955. (h) Andersen, L.; Mikkelsen, L. M.; Beau, J.-M.; Skrydstrup, T. *Synlett* **1998**, 1393. (i) Jarreton, O.; Skrydstrup, T.; Espinosa, J.-F.; Jiménez-Barbero, J.; Beau, J.-M. *Chem. Eur. J.* **1999**, *5*, 430. (j) Krintel, S. L.; Jiménez-Barbero, J.; Skrydstrup, T. *Tetrahedron Lett.* **1999**, *40*, 7565. (k) Mikkelsen, L. M.; Krintel, S. L.; Jiménez-Barbero, J.; Skrydstrup, T. *Chem. Commun.* **2000**, 2319. (i) Mikkelsen, L. M.; Krintel, S. L.; Jiménez-Barbero, J.; Skrydstrup, T. *J. Org. Chem.* **2002**, 67, 6287.

(8) Miquel, N.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4111.

(9) (a) Vlahov, I. R.; Vlahova, P. I.; Linhardt, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 1480. (b) Bazin, H. G.; Du, Y.; Polat, T.; Linhardt, R. J. *J. Org. Chem.* **1999**, *64*, 7254.

10.1021/jo020585a CCC: $25.00
Published on Web 02/01/2003

SCHEME 1

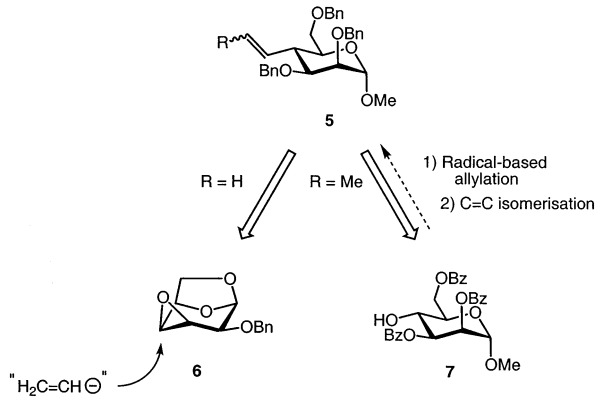


known *O*-glycosylations. Exploiting the previous work on cyclic oligosaccharide synthesis,[3] we therefore set out to prepare an α-*C*-cyclodextrin analogue in which all of the six etheral linkages have undergone an O to CH_2 exchange. In this paper, we reveal our first steps for achieving this goal through the demonstration that the crucial α-(1→4) linkage between the connecting pyranosides can indeed be achieved by employing the low-valent lanthanide reagent, samarium diiodide.

Results and Discussion

Retrosynthetic Considerations. Our target cyclic *C*-oligosaccharide **1** is illustrated in Scheme 1, assembled with six α-(1→4)-mannopyranoside units. This choice is based on (1) the previous syntheses of cyclic mannooligosaccharides and the known capacity for appropriately functionalized linear oligomers of mannose to undergo cyclization upon treatment under standard glycosylation conditions[3] and (2) the 1,2-trans selectivity obtained in the SmI_2-induced *C*-glycosylations,[7a,b,d,e,i−k,8] implying that for α-selectivity at the anomeric carbon, an axially oriented C2-substituent is required as is the case for mannopyranosides. In the retrosynthetic analysis of such a *C*-glycoside analogue, it is nevertheless tempting to speculate whether a suitably functionalized *C*-disaccharide **2** possessing a C1−Sm bond, as well as the acceptor at C4′, could undergo a trimerization process to the desired macrocycle after deoxygenation. Similar cyclization approaches have been successfully employed by Stoddart and co-workers for the synthesis of nonnatural cyclic oligosaccharides via *O*-glycosylation.[10] Although higher oligomers could also be anticipated, the number of steps leading to **1** via a linear synthesis would be dramatically reduced upon the successful outcome of this cyclization step.

SCHEME 2



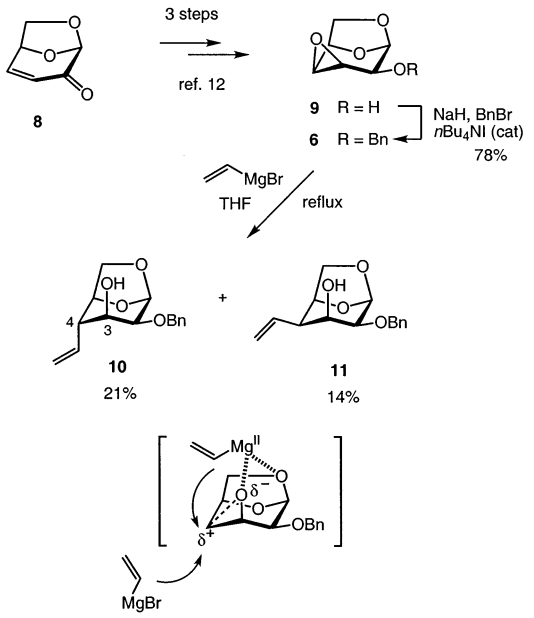
Pertinent for this approach, however, is whether the *C*-α-(1→4) linkage can be formed employing a mannosyl anomeric samarium species. We have earlier observed the detrimental influence of sterical hindrance on some of the SmI_2-promoted *C*-glycosylations.[7i] As *O*-glycosylation of the C4−OH group in gluco- and mannopyranosides is generally one of the most demanding to perform due to the sterical environment surrounding this hydroxyl group, it was anticipated that the *C*-glycosylation step could experience similar difficulties. It is therefore crucial for the successful outcome of the cyclization that this C−C bond-forming step can be performed in the synthesis of the *C*-disaccharide building block **2**. Access to the *C*-glycosyl donor and acceptor, **3** and **4**, respectively, was envisaged to come from the same *C*-branched methyl mannoside **5**. Hence, the synthesis of **2** first boils down to the introduction of an equatorially oriented formyl group equivalent at the C4-position of methyl 4-deoxymannopyranoside.

Two routes were esteemed possible for achieving this transformation as shown in Scheme 2. The first route exploits the known preference for trans-diaxial opening of epoxides in 1,6-anhydrosugars such as **6** with nucleophiles. On the other hand, radical-based allylation at C4 with the partially protected mannopyranoside **7** was predicted to be selective for the equatorial position. Subsequent migration of the carbon−carbon double bond to the internal position was expected to give the desired precursor.

The 1,6-Anhydrosugar Approach. Synthesis of the required 1,6:3,4-dianhydro-*β*-talopyranose **9** has previ-

(10) (a) Ashton, P. R.; Brown, C. L.; Menzer, S.; Nepogodiev, S. A.; Stoddart, J. F.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 580. (b) Ashton, P. R.; Cantrill, S. J.; Gattuso, G.; Menzer, S.; Nepogodiev, S. A.; Shipway, A. N.; Stoddart, J. F.; Williams, D. J. *Chem. Eur. J.* **1997**, *3*, 1299. For other examples of other linkages, see ref 3.

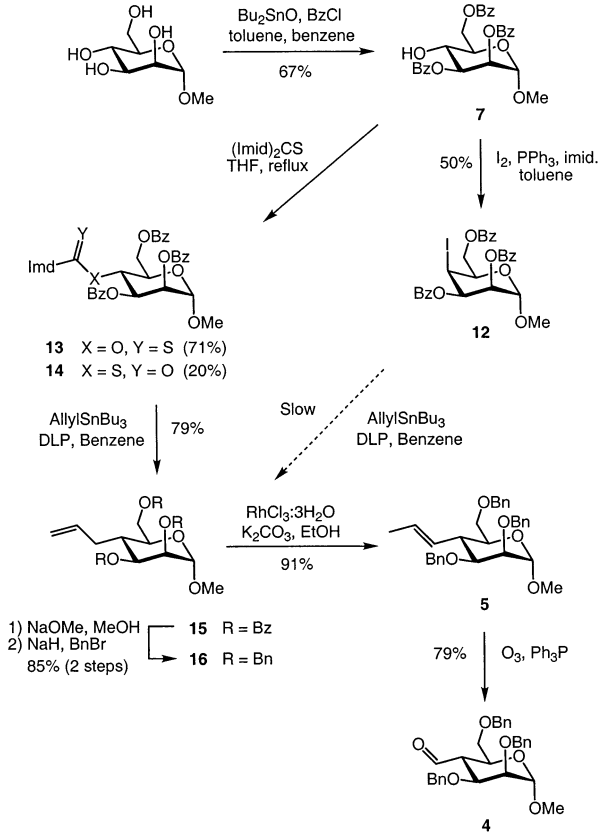
SCHEME 3



ously been reported in three steps[11] starting from the readily available levoglucosenone **8**.[12] In this work, the selective reduction of the ketone followed by an iodoacetylation step and concomitant ring closure under basic conditions was reported to afford the epoxide **9** in high yields (Scheme 3). However, in our hands, the latter two steps proved less effective and typical yields of this sequence were of the order of 30−40%. For the introduction of the formyl group precursor at C4, a regioselective opening of **6** was attempted with vinylmagnesium bromide.[13] In contrast to our previous work on a similar case,[7i] refluxing a solution of the Grignard reagent with **6** produced two alkene-containing products in a ratio of 3:2 which could be separated by column chromatography. Whereas the major product was identified as the desired alkene **10**, the second proved to be the C4-epimer **11** rather than the C3-functionalized anhydrosugar. The low and unexpected regioselectivity could be the result of a strong coordination of the magnesium ion to both anhydro oxygens in the concave cavity of **6** (Scheme 3), resulting in partial epoxide opening and transfer of the vinyl group to the more hindered face of the cation intermediate.

Other conditions were also examined in an attempt to improve the selectivity of the epoxide opening, although in vain.[14] Hence, this route was abandoned and recourse was taken to introduce a formyl group precursor via a radical-based allylation followed by migration of the C−C double bond. This approach was inspired by the recent work of Postema et al. in their synthesis of several *β-C*-disaccharides.[15]

SCHEME 4



The Radical Allylation Approach. The preparation of the 2,3,6-tri-*O*-benzoate of methyl mannopyranoside was achieved with benzoyl chloride and dibutyltin oxide with use of a procedure recently reported for the synthesis of the same tribenzoate in the *gluco*-series.[16] This selective benzoylation procedure of methyl α-D-mannopyranoside afforded the tribenzoate **7** in 67% yield (Scheme 4). A standard Garegg iodination procedure converted the remaining secondary alcohol to its corresponding iodide **12** with inversion of configuration at C4.[17] Attempted allylation at this position with allyltributyltin and AIBN or DLP in refluxing toluene as earlier described in the *gluco*-series resulted in a slow reaction that was not complete after 72 h. Although the desired *C*-branched sugar was obtained, substantial amounts of the 4-deoxy derivative were also produced. Attributing this sluggishness to the 1,3-diaxial relationship between the iodide and the C2-benzoate, we decided to convert alcohol **7** to its corresponding thionocarbamate and thereby perserve the equatorial position of the C4-substituent.

Treatment of alcohol **7** with *N*,*N*′-thiocarbonyldiimidazole in THF or acetonitrile in the presence of DMAP (cat.) produced, however, two separable products possessing identical mass and almost matching ^{1}H and ^{13}C

(11) (a) Matsumoto, K.; Ebata, T.; Koseki, K.; Okano, K.; Kawakami, K.; Matsushita, H. *Heterocycles* **1992**, *34*, 1935. (b) Matsumoto, K.; Ebata, T.; Koseki, K.; Okano, K.; Kawakami, K.; Matsushita, H. *Carbohydr. Res.* **1993**, *246*, 345.

(12) Prepared by pyrolysis of acid-treated cellulose or newspaper clippings. (a) Isobe, M.; Fukuda, Y.; Nishikawa, T.; Chabert, P. *Tetrahedron Lett.* **1990**, *31*, 3327. (b) Shafizadeh, F.; Chin, P. P. S. *Carbohydr. Res.* **1977**, *58*, 79.

(13) Inghardt, T.; Frejd, T. *Synthesis* **1990**, 285.

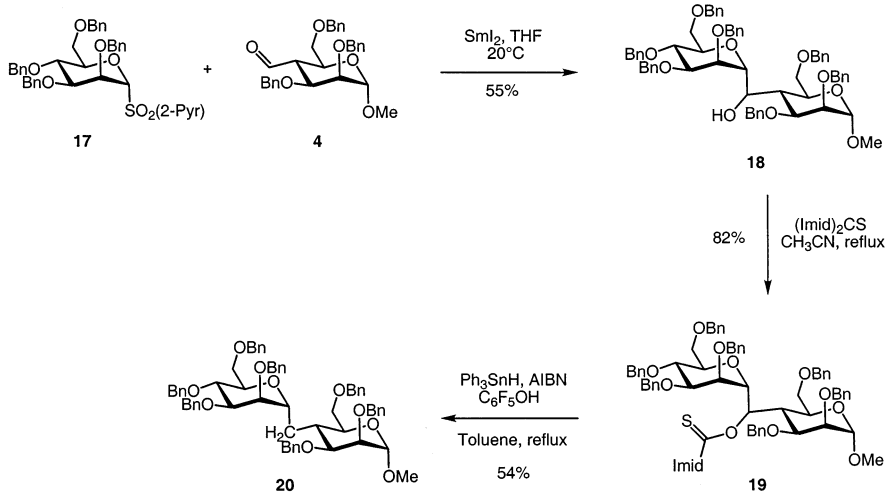
(14) Similar attempts to open the epoxyalcohol **9** with vinylmagnesium bromide led to a complex mixture of products.

(15) (a) Liu, L.; Postema, M. H. D. *J. Am. Chem. Soc.* **2001**, *123*, 8602. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

(16) Hakamata, W.; Nishio, T.; Oku, T. *Carbohydr. Res.* **2000**, *324*, 107. See also: Chowdhary, M. S.; Jain, R. K.; Rana, S. S.; Matta, K. L. *Carbohydr. Res.* **1986**, *152*, 323.

(17) Garegg, P.; Johansson, R.; Ortega, C.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 681.

SCHEME 5



NMR spectra. Both ^{1}H NMR spectra displayed the characteristic peaks for the three imidazolyl protons (8.25−6.80 ppm) where the greatest difference was observed for the H4-proton appearing at 6.74 and 6.19 ppm. The two products were therefore assigned to the thionocarbamate **13** and its corresponding thiocarbamate **14**, resulting from a C═S to C═O rearrangement (Scheme 4). The best conditions for obtaining the thionocarbamate were produced when using THF as the solvent, affording a 71% yield of **13** whereas only 20% of the isomer **14** could be isolated. Although this type of rearrangment is typically observed for systems involving the hydroxyl group connected to an activated carbon, this is not the case for **7**. We have previously noted the same rearrangement in our attempt to prepare a thionocarbonate of a sterically hindered secondary alcohol.[7i] As the C4-hydroxyl groups of the sugar rings are in general more demanding to functionalize compared to the adjacent groups, the driving force behind this rearrangement is most probably a combination of the strain released on going from the C4−O single bond to the corresponding but longer C4−S bond and the formation of the stronger C═O bond.[18]

Subjecting **13** to allyl tributyltin and dilauoryl peroxide (DLP) in refluxing benzene led to the isolation of the C4-allyl branched sugar in a satisfactory 79% yield. Only the equatorially allylated product **15** could be identified from the reaction mixture, which contradicts similar allylations in the *gluco*-series where epimeric C4 mixtures were obtained in favor of the equatorial product. This increased selectivity observed for mannose is explained by the unfavorable approach of the incoming allyl group from above the carbohydrate ring due to sterical interactions with the axially oriented C2-substituent.[19]

The benzoyl groups were subsequently exchanged for benzyl groups to give compound **16**. Migration of the double bond to give the internal alkene **5** was accomplished in excellent yield by treatment with rhodium trichloride trihydrate (10%) and potassium carbonate in boiling ethanol.[20] The *E*-configuration of the double bond was produced almost exclusively as seen by the characteristic trans-coupling constant of 15.2 Hz. Finally, ozonolysis of the olefin produced the *C*-formyl branched monosaccharide **4** in high yield.

Completion of the Synthesis of the *C*-Disaccharide. The crucial coupling step was achieved by adding dropwise a freshly prepared 0.1 M solution of SmI_2 in THF to a solution of the aldehyde **4** and 4 equiv of the previously reported 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl 2′-pyridyl sulfone (**17**) in the same solvent at room temperature (Scheme 5).[7e] An immediate decolorization of the low-valent lanthanide reagent was noted until all the pyridyl sulfone had been consumed signaling completion of the reaction. The *C*-disaccharide **18** could thereby be isolated in 55% yield as a single stereoisomer at the two newly formed stereogenic centers as determined by ^{1}H NMR spectroscopy. This yield was quite satisfactory and corresponded well with other coupling yields performed at C2-, C3-, and C6-positions of previous *C*-formyl branched mannopyranosides tested,[7a,b,e,i−l] implying that sterical hindrance is not a problem at C4 as was initially anticipated.

Finally, the newly formed hydroxyl group was removed by a two-step sequence previously reported in the deoxygenation of other *C*-oligosaccharides.[7e,i−l] First, **18** was converted to its thionocarbonate **19** upon subjecting the secondary alcohol to a large excess of thiocarbonyldiimidazole in refluxing acetonitrile followed by the slow removal of the solvent upon heating. We have previously noted the difficulties in functionalizing this position in other *C*-disaccharides, hence explaining the use of these unorthodox conditions. Subsequent application of our method for deoxygenating these sterically hindered secondary alcohols employing triphenyltin hydride, AIBN (cat.), and pentafluorophenol in refluxing toluene yielded the desired heptabenzylated *C*-disaccharide **20** in 54% yield.

Conclusions

We have rapidly assembled the *C*-linked disaccharide α-D-Man-(1→4)-D-Man via the coupling of a mannosyl

(18) Barton, D. H. R.; Fontana, G.; Yang, Y. *Tetrahedron* **1996**, *52*, 2705 and references therein.

(19) The isomer **14** could not be transformed to **15** under identical reaction conditions.

(20) (a) Warmerdam, E.; Tranoy, I.; Renoux, B.; Gesson, J.-P. *Tetrahedron Lett.* **1998**, *39*, 8077. (b) Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

anomeric samarium species with the C4-formyl branched mannopyranoside as the key step. The successful outcome of this coupling step lends support for the use of this reaction in trimerization of an appropriately functionalized α-D-Man-(1→4)-D-Man disaccharide to its corresponding cyclic *C*-oligosaccharide. Further work is now required to prepare a C4-branched mannosyl donor, which will allow introduction of a new formyl group in the *C*-disaccharide.

Experimental Section

General Methods. THF was dried and freshly distilled over sodium/benzophenone. Dichloromethane was freshly distilled over P_2O_5. HMPA was dried over CaH_2 and distilled. DMF was distilled and stored over molecular sieves (4 Å). Samarium diiodide was prepared according to the literature.[21] 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl 2′-pyridyl sulfone (**17**) was prepared as previously reported.[7e]

Methyl 2,3,6-Tri-*O*-benzoyl-α-D-mannopyranoside (7). Methyl α-D-mannopyranoside (200 mg, 1.03 mmol) and dibutyltin oxide (769 mg, 3.09 mmol) were dissolved in toluene and benzene (1:1, 100 mL) and the mixture was refluxed in a Dean−Stark apparatus until approximately 80 mL of the solvent was distilled off. After the solution was cooled to 20 °C benzoyl chloride (400 μL, 3.40 mmol) was added, and the mixture was stirred for 3 h at 20 °C and then at 100 °C overnight. The solvent was then evaporated off in vacuo and acetonitrile (20 mL) was added. The acetonitrile phase was washed twice with pentane and then concentrated to dryness in vacuo. The residue was purified by column chromatography (EtOAc:pentane, 1:7) yielding 347 mg of the tribenzoate **7** as a colorless powder (67%). ^{1}H NMR (200 MHz): δ 8.16−7.89 (5H, m), 7.66−7.25 (10H, m), 5.70−5.59 (2H, m), 4.93 (1H, br d), 4.91 (1H, dd, *J* = 3.8, 12.4 Hz), 4.65 (1H, dd, *J* = 2.0, 12.4 Hz), 4.28 (1H, ddd, *J* = 5.0, 10.2, 10.2 Hz), 4.10 (1H, ddd, *J* = 2.0, 3.8, 10.2 Hz), 3.45 (3H, s), 3.02 (1H, d, *J* = 5.0 Hz). ^{13}C NMR (50 MHz): δ 167.0, 166.8, 165.5, 133.6, 133.5, 133.4, 130.0−128.5, 98.9, 72.8, 71.3, 70.7, 66.4, 63.6, 55.5. IR (KBr, disk): 3500, 1730−1720, 1452, 1273, 1102, 1069 cm^{-1}. HR-MS (ES-TOF): calcd for $C_{28}H_{26}NaO_9$ (M + Na) 529.1474, found 529.1472.

Methyl 2,3,6-Tri-*O*-benzoyl-4-*O*-thiocarbonylimidazolyl-α-D-mannopyranoside (13). Methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (**7**) (500 mg, 0.99 mmol) and thiocarbonyldiimidazole (352 mg, 1.98 mmol) were dissolved in dry distilled THF (5 mL) and the solution was refluxed overnight. After being cooled to 20 °C, the mixture was evaporated in vacuo and the residue was purified by column chromatography (EtOAc:pentane, 1:5 to 1:2) yielding 432 mg of the thionocarbamate **13** as a colorless powder (71%). ^{1}H NMR (200 MHz): δ 8.26 (1H, dd, *J* = 0.8, 0.8 Hz), 8.12−8.06 (4H, m), 7.85−7.79 (2H, m), 7.67−7.25 (10H, m), 6.96 (1H, dd, *J* = 0.8, 1.8 Hz), 6.74 (1H, dd, *J* = 9.6, 9.8 Hz), 6.01 (1H, dd, *J* = 3.4, 9.8 Hz), 5.71 (1H, dd, *J* = 1.8, 3.4 Hz), 5.03 (1H, d, *J* = 1.8 Hz), 4.73 (1H, dd, *J* = 4.4, 13.6 Hz), 4.54−4.61 (1H, m), 4.50 (1H, dd, *J* = 4.0, 13.6 Hz), 3.52 (3H, s). ^{13}C NMR (50 MHz): δ 183.4, 166.2, 165.4, 165.4, 133.7, 133.8, 133.7, 133.5, 131.3, 130.0−128.6, 118.1, 98.8, 75.4, 70.7, 69.9, 68.3, 62.7, 56.0. IR (KBr, disk): 1730−1720, 1394, 1270, 1109 cm^{-1}. HR-MS (ES-TOF): calcd for $C_{32}H_{28}N_2NaO_9S$ (M + Na) 639.1413, found 639.1414.

Further elution of the column gave the thiocarbamate **14** (121 mg, 20%) as a light yellow powder. ^{1}H NMR (200 MHz): δ 8.15−7.92 (7H, m), 7.61−7.48 (3H, m), 7.43−7.32 (7H, m), 6.84 (1H, dd, *J* = 0.8, 1.6 Hz), 6.32 (1H, dd, *J* = 3.2, 10.0 Hz), 6.19 (1H, dd, *J* = 9.8, 10.0 Hz), 5.84 (1H, dd, *J* = 1.8, 3.2 Hz), 5.01 (1H, d, *J* = 1.8 Hz), 4.75 (1H, bd, *J* = 10.2 Hz), 4.49 (1H, dd, *J* = 4.2, 10.2 Hz), 4.47−4.40 (1H, m), 3.54 (3H, s). ^{13}C NMR (50 MHz): δ 182.7, 166.2, 165.5, 165.4, 137.2, 134.0, 133.4, 133.5, 131.1, 130.1−128.7, 118.0, 98.9, 78.4, 69.3, 68.8, 66.5, 62.7, 56.0. IR (KBr, disk): 1728−1720, 1289, 1279 cm^{-1}. HR-MS (ES-TOF): calcd for $C_{32}H_{28}N_2NaO_9S$ (M + Na) 639.1413, found 639.1414.

Methyl 2,3,6-Tri-*O*-benzoyl-4-deoxy-4-*C*-allyl-α-D-mannopyranoside (15). Allyl tributylstannane (149 μL, 0.49 mmol) was added to the thionocarbamate **13** (100 mg, 0.16 mmol) dissolved in degassed benzene (3.0 mL). The mixture was refluxed overnight, during which time a catalytic amount of dilauroryl peroxide (DLP, 13 mg, 0.032 mmol) was added in small portions. The solvent was removed in vacuo and the residue was redissolved in MeCN (10 mL) and then washed twice with pentane. Evaporation to dryness and column chromatography (EtOAc:pentane, 1:15) yielded **15** as a colorless oil (68 mg, 79%). ^{1}H NMR (200 MHz): δ 8.16−8.02 (4H, m), 7.96−7.90 (2H, m), 7.66−7.30 (9H, m), 5.87 (1H, ddt, *J* = 7.6, 10.0, 17.4 Hz), 5.66 (1H, dd, *J* = 3.0, 11.4 Hz), 5.52 (1H, dd, *J* = 1.8, 3.0 Hz), 5.08 (1H, br d, *J* = 17.4 Hz), 5.06 (1H, br d, *J* = 10.0 Hz), 4.94 (1H, d, *J* = 1.8 Hz), 4.66 (1H, d, *J* = 2.4 Hz), 4.65 (1H, d, *J* = 3.6 Hz), 4.13 (1H, ddd, *J* = 2.4, 3.6, 11.2 Hz), 3.47 (3H, s), 2.73 (1H, ddt, *J* = 4.2, 11.2, 11.4 Hz), 2.40−2.32 (2H, m). ^{13}C NMR (50 MHz): δ 166.5, 165.6, 165.6, 133.6, 133.4, 133.3, 133.2, 130.2−128.5, 118.6, 99.1, 69.7, 69.4, 69.1, 64.5, 55.5, 36.2, 31.1. HR-MS (ES-TOF): calcd for $C_{31}H_{30}NaO_8$ (M + Na) 553.1838, found 553.1834.

Methyl 4-*C*-Allyl-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-mannopyranoside (16). A catalytic amount of freshly prepared NaOMe in MeOH was added to the tribenzoate **15** (470 mg, 0.89 mmol) dissolved in MeOH (10 mL). The solution was stirred for 5 h at 20 °C and then neutralized by the addition of a small piece of dry ice. Evaporation and coevaporation twice with toluene yielded the crude methyl 4-deoxy-4-*C*-allyl-α-D-mannopyranoside, which was redissolved in DMF (15 mL) and then cooled to 0 °C. NaH (213 mg, 5.31 mmol) was added portionwise with stirring. After 10 min, benzyl bromide (631 μL, 5.31 mmol) was added and the mixture was stirred overnight. After dilution with diethyl ether, the organic phase was washed four times with water, dried ($MgSO_4$), and concentrated to dryness in vacuo. Column chromatography (EtOAc:pentane, 1:10) yielded 367 mg of **16** as a colorless oil (85% for two steps). ^{1}H NMR (400 MHz): δ 7.38−7.23 (15H, m), 5.66 (1H, ddt, *J* = 7.0, 10.2, 17.2 Hz), 4.95−4.83 (2H, m), 4.83 (1H, d, *J* = 1.8 Hz), 4.69 (2H, s), 4.55 (1H, d, *J* = 12.2 Hz), 4.54 (1H, d, *J* = 12.2 Hz), 4.51 (1H, d, *J* = 11.6 Hz), 4.34 (1H, d, *J* = 11.6 Hz), 3.76−3.61 (5H, m), 3.37 (3H, s), 2.51−2.33 (2H, m), 2.18−2.03 (1H, m). ^{13}C NMR (50 MHz): δ 138.7 (2C), 138.5, 135.2, 128.6−127.6, 117.2, 99.6, 75.9, 73.5, 72.6, 72.2, 71.6, 71.1, 70.9, 55.1, 37.1, 30.9. IR ($CHCl_3$, film): 3018, 2917, 2400, 1363, 1216 cm^{-1}. HR-MS (ES-TOF) *m*/*z*: calcd for $C_{31}H_{36}NaO_5$ (M + Na) 511.2460, found 511.2462.

Methyl 2,3,6-Tri-*O*-benzyl-4-deoxy-4-*C*-(1-*E*-prop-1-enyl)-α-D-mannopyranoside (5). A solution of the alkene **16** (349 mg, 0.71 mmol), solid K_2CO_3 (18 mg, 0.13 mmol, 18 mol %), and $RhCl_3$:$3H_2O$ (18.8 mg, 0.071 mmol, 10 mol %) in EtOH (96%, 8.0 mL) was heated to reflux for 2.5 h, whereafter the solvent was removed in vacuo. Saturated aqueous NaCl was added and the mixture was extracted three times with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (EtOAc:pentane, 1:10) yielded 319 mg (91%) of the internal alkene **5** as a colorless oil. ^{1}H NMR (200 MHz): δ 7.40−7.24 (15 H, m), 5.59 (1H, dq, *J* = 6.6, 15.2 Hz), 5.03 (1H, ddq, *J* = 1.6, 9.2, 15.2 Hz), 4.81 (1H, d, *J* = 1.8 Hz), 4.73 (2H, s), 4.61 (1H, d, *J* = 12.2 Hz), 4.53 (1H, d, *J* = 12.2 Hz), 4.51 (1H, d, *J* = 12.1 Hz), 4.38 (1H, d, *J* = 12.1 Hz), 3.71−3.52 (5H, m, H2, H3, H5), 3.34 (3H, s), 2.77 (1H, ddd, *J* = 9.2, 10.4, 10.4 Hz), 1.64 (1H, dd, *J* = 1.6, 6.6 Hz). ^{13}C NMR (50 MHz): δ 138.8, 138.8, 138.7, 129.8, 128.8, 128.5−127.5, 77.5, 73.5, 72.7, 72.3, 72.1, 71.7, 71.4, 54.9, 43.1, 18.4. HR-MS (ES-TOF): calcd for $C_{31}H_{36}NaO_5$ (M + Na) 511.2460, found 511.2459.

(21) Namy, J. L.; Girard, P.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

Methyl 2,3,6-Tri-*O*-benzyl-4-deoxy-4-*C*-formyl-α-D-mannopyranoside (4). The alkene **5** (60 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (4.0 mL) and MeOH (1.0 mL) and cooled to −78 °C. Ozone was bubbled through the solution for 2−3 min until the color changed to light blue. Excess ozone was then removed by bubbling argon through the cold solution for 5 min. Triphenyl phosphine (74 mg, 0.28 mmol) was added and after being stirred for 10 min at −78 °C the reaction was warmed to 20 °C and stirred for an additional hour. Evaporation to dryness and column chromatography (EtOAc:pentane, 1:7) yielded 50.0 mg (85%) of **4** as a colorless oil. The aldehyde was used immediately in the following step. ^{1}H NMR (200 MHz): δ 9.76 (1H, d, J = 3.0 Hz), 7.36−7.23 (15H, m), 4.79 (1H, d, J = 1.8 Hz), 4.71 (2H, s), 4.57 (1H, d, J = 11.8 Hz), 4.54 (1H, d, J = 11.4 Hz), 4.48 (1H, d, J = 11.4 Hz), 4.35 (1H, d, J = 11.8 Hz), 4.17 (1H, dd, J = 3.0, 11.2 Hz), 4.05 (1H, ddd, J = 5.0, 5.2, 10.2 Hz), 3.74 (1H, dd, J = 2.0, 3.0 Hz), 3.65−3.59 (2H, m), 3.42−3.35 (1H, m), 3.33 (3H, s). ^{13}C NMR (50 MHz): δ 202.5, 138.4, 138.1, 137.9, 128.8−127.6, 99.6, 75.3, 73.7, 72.9, 71.7, 71.6, 71.2, 68.7, 55.3, 52.4. IR (KBr, disk): 3080−3010, 2914, 1727, 1505, 1454, 1114, 1075 cm^{-1}. HR-MS (ES-TOF): calcd for $C_{29}H_{32}NaO_6$ (M + Na) 499.2097, found 499.2097.

Methyl 2,3,6-Tri-*O*-benzyl-4-deoxy-4-*C*-(1′-(2′,3′,4′,6′-tetra-*O*-benzyl-1′-deoxy-α-D-mannopyranosyl)hydroxymethylene)-α-D-mannopyranoside (18). Samarium diiodide (0.10 M in THF, 4.2 mL, 0.42 mmol) was added dropwise to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl 2-pyridyl sulfone (**17**) (111.7 mg, 0.17 mmol) and aldehyde **4** (20.0 mg, 0.042 mmol) in THF (1.0 mL) under an argon atmosphere until a persistent dark blue color was obtained. The mixture was stirred at 20 °C for 10 min and then quenched by the addition of saturated aqueous NH_4Cl. The mixture was diluted with CH_2Cl_2 and the aqueous phase was extracted once with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (EtOAc:pentane, 1:5 to 1:3) yielded 23.3 mg of the *C*-disaccharide **18** (55%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.16 (35H, m), 4.84 (1H, d, J = 2.4 Hz), 4.70 (2H, s), 4.56 (1H, d, J = 12.0 Hz), 4.56 (1H, d, J = 12.0 Hz), 4.50 (1H, d, J = 10.4 Hz), 4.50 (1H, d, J = 10.4 Hz), 4.47 (1H, d, J = 12.4 Hz), 4.45 (1H, d, J = 12.0 Hz), 4.44 (1H, d, J = 11.6 Hz), 4.43 (1H, d, J = 12.0 Hz), 4.42 (1H, d, J = 12.4 Hz), 4.39 (1H, d, J = 11.2 Hz), 4.39 (1H, d, J = 11.6 Hz), 4.38 (1H, d, J = 11.2 Hz), 4.25 (2H, m), 4.03 (1H, dd, J = 2.8, 6.4 Hz), 4.03 (1H, m), 3.95 (1H, dd, J = 4.0, 6.4 Hz), 3.91 (1H, m), 3.84 (1H, dd, J = 7.2; 10.0 Hz), 3.80 (1H, dd, J = 2.8; 3.0 Hz), 3.76 (1H, dd, J = 2.4, 2.4 Hz), 3.72−3.68 (2H, m), 3.61 (1H, dd, J = 3.0, 10.0 Hz), 3.33 (3H, s), 2.72 (1H, m). ^{13}C NMR (50 MHz): δ 138.9, 138.8, 138.7, 138.7, 138.5, 138.5, 138.3, 128.7−127.5, 99.7, 78.2, 75.1, 74.5, 73.7, 73.5, 73.5, 73.2, 72.7, 72.7, 72.5, 72.3, 72.1, 71.3, 71.3, 71.2, 69.8, 69.2, 66.9, 55.0, 39.8. HR-MS (ES-TOF): calcd for $C_{63}H_{68}NaO_{11}$ (M + Na) 1023.4659, found 1023.4658.

Methyl 2,3,6-Tri-*O*-benzyl-4-deoxy-4-*C*-(1′-(2′,3′,4′,6′-tetra-*O*-benzyl-1′-deoxy-α-D-mannopyranosyl)oxythiocarbonylimidazolylmethylene)-α-D-mannopyranoside (19). The *C*-disaccharide **18** (23 mg, 0.023 mmol) and thiocarbonyl diimidazole (82 mg, 0.46 mmol) dissolved in acetonitrile (3.0 mL) were refluxed overnight. Evaporation in vacuo and column chromatography (EtOAc:pentane, 1:2) yielded 21.0 mg of **19** as a yellow oil (82%). ^{1}H NMR (400 MHz): δ 8.28 (1H, s), 7.47 (1H, br s), 7.40−7.02 (35H, m), 6.94 (1H, br s), 6.65 (1H, br d, J = 8.4 Hz), 4.88 (1H, d, J = 1.4 Hz), 4.72 (1H, d, J = 11.6 Hz), 4.68 (1H, d, J = 11.6 Hz), 4.65 (1H, d, J = 11.6 Hz), 4.63 (1H, d, J = 10.0 Hz), 4.56 (1H, d, J = 11.6 Hz), 4.55 (1H, d, J = 11.2 Hz), 4.53 (1H, d, J = 10.8 Hz), 4.43 (1H, d, J = 12.0 Hz), 4.41 (1H, d, J = 10.0 Hz), 4.38 (1H, d, J = 11.2 Hz), 4.32 (1H, d, J = 12.0 Hz), 4.27 (1H, d, J = 12.0 Hz), 4.21 (1H, d, J = 12.0 Hz), 4.18 (1H, d, J = 10.8 Hz), 4.15 (1H, m), 3.92−3−73 (9H, m), 3.65 (1H, dd, J = 5.2, 10.4 Hz), 3.53 (1H, dd, J = 2.8, 10.4 Hz), 3.34 (3H, s), 2.81 (1H, br dd, J = 10.0, 10.4 Hz). ^{13}C NMR (50 MHz): δ 185.1, 138.8, 138.8, 138.6, 138.6, 138.5, 138.4, 137.8, 137.7, 131.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 127.9, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 118.3, 99.6, 77.5, 76.3, 75.6, 74.9, 74.8, 74.4, 74.1, 73.4, 73.4, 73.3, 73.0, 72.3, 72.0, 71.8, 71.8, 71.8, 70.1, 69.4, 55.5, 38.5. HR-MS (ES-TOF): calcd for $C_{67}H_{70}N_2NaO_{11}S$ (M + Na) 1134.4598, found 1134.4592.

Methyl 2,3,6-Tri-*O*-benzyl-4-deoxy-4-*C*-(1′-(2′,3′,4′,6′-tetra-*O*-benzyl-1′-deoxy-α-D-mannopyranosyl)methylene)-α-D-mannopyranoside (20). A mixture of the thionocarbamate **19** (21 mg, 0.019 mmol), pentafluorophenol (7 mg, 0.038 mmol), triphenyltin hydride (15 μL, 0.057 mmol), and a catalytic amount of AIBN (2 mg) in toluene (4.0 mL) was refluxed for 3 h and then evaporated in vacuo. The residue was redissolved in acetonitrile and washed two times with pentane. Evaporation to dryness and column chromatography (EtOAc:pentane, 1:5) yielded 10.0 mg of the *C*-disaccharide **20** as a colorless oil (54%). ^{1}H NMR (400 MHz): δ 7.38−7.13 (35H, m), 4.85 (1H, d, J = 1.4 Hz), 4.73 (1H, d, J = 11.2 Hz), 4.68 (1H, d, J = 12.4 Hz), 4.64 (1H, d, J = 12.4 Hz), 4.62 (1H, d, J = 12.4 Hz), 4.55 (1H, d, J = 13.2 Hz), 4.51 (1H, d, J = 10.4 Hz), 4.49 (1H, d, J = 13.2 Hz), 4.47 (1H, d, J = 11.6 Hz), 4.46 (1H, d, J = 11.2 Hz), 4.42 (1H, d, J = 12.4 Hz), 4.37 (1H, d, J = 10.4 Hz), 4.35 (1H, d, J = 12.4 Hz), 4.28 (1H, d, J = 12.4 Hz), 4.22 (1H, d, J = 11.6 Hz), 4.25−4.18 (2H, m), 3.85 (1H, dd, J = 7.6, 8.0 Hz), 3.80−3.62 (8H, m), 3.36 (3H, s), 2.27 (1H, m), 1.61−1.54 (2H, m). ^{13}C NMR (50 MHz): δ 138.9−138.5, 128.5−127.6, 99.7, 78.7, 78.6, 76.2, 76.0, 75.3, 74.4, 73.1, 73.0, 72.6, 72.4, 72.2, 71.8, 71.8, 71.6, 71.6, 71.2, 69.9, 55.2, 35.5, 28.2. HR-MS (ES-TOF): calcd for $C_{63}H_{68}NaO_{10}$ (M + Na) 1007.4710, found 1007.4710.

Acknowledgment. We are indebted to the Danish National Science Foundation (THOR Program), the University of Aarhus, and the Carlsberg Foundation for generous financial support.

Supporting Information Available: ^{1}H NMR spectra for compounds **4**, **5**, **13**−**16**, and **18**−**20** and ^{13}C NMR spectra for **4**, **5**, **13**−**16**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020585A