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Synthesis of 2-*O*-(3-*O*-Carbamoyl-α-D-mannopyranosyl)-L-gulopyranose: Sugar Moiety of Antitumor Antibiotic Bleomycin

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Abstract: A new route to the disaccharide moiety (2-O-(3-O-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose) of the antitumor agent bleomycin was developed. Both the L-gulose synthon 21 and the 3-O-carbamoyl-D-mannose segment 30 were prepared from D-mannose in a regioselective manner by applying stannylene acetal methodology. Glycosylation of 21 with 30 proceeded smoothly, and further conversion to disaccharide derivatives (33 and 34) was successfully accomplished. © 1997 Elsevier Science Ltd.

The bleomycins (BLMs) are a family of glycopeptide antitumor antibiotics isolated from the fermentation broth of *Streptomyces verticillus* in 1966 by Umezawa *et al.*,[1] and currently used for the clinical treatment of Hodgkin's lymphoma, carcinomas of the skin, head, and neck, and tumors of the testis.[2] Cleavage of DNA by BLM in the presence of oxygen and ferrous ion occurs preferentially at G-C (5'→3') and G-T (5'→3') sequences, and is responsible for its antitumor activity.[3] BLM is a glycopeptide having a unique hexapeptide and a disaccharide.[4] We have been carrying out a synthetic approach to define the role of each segment through the synthesis of model compounds.[5] Our attention has been focused on (1) the metal binding site, pyrimidoblamic acid connected to a hydroxyhistidine moiety,[6] and (2) the DNA binding site, the bithiazole and linker moieties.[7] Based on these studies of structure-function relationships, G-specific and AT-specific BLM analogues (PYML-6 and PYML(6)-(AHM)-distamycin, respectively) were successfully synthesized.[7] Although these analogues showed potent DNA cleaving activity with the controlled sequence specificity, they were less cytotoxic against tumor cells in suspension culture than BLM. The significant decrease in cytotoxicity of BLM analogues in a cell system is apparently due to the lack of a disaccharide moiety in those analogues, in which a *tert*-butyl group is introduced instead. Because BLM localizes specifically in tumor cells in man and other animals[3c,8], allowing ^{57}Co-BLM to be used clinically as a cancer diagnostic drug,[8b] the

This paper is dedicated to Prof. Samuel J. Danishefsky with sincere gratitude for all the inspiration and encouragement he provided over the years.

disaccharide moiety of BLM has been hypothesized to be significant not only for the formation of a molecular cavity to accommodate dioxygen but also for molecular recognition at cell surfaces. All of the model compounds ("designed Bleomycins") we have prepared so far have a *tert*-butyl group, and by these models we could demonstrate the role of the disaccharide moiety as a bulky steric factor to accommodate dioxygen. However, this seems to be only one of several functions of the disaccharide moiety. In order to investigate another important role of the disaccharide moiety,[9] *i.e.*, cell permeability and molecular recognition at cell surfaces, it became necessary to develop a practical method for the synthesis of the disaccharide, 2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose.

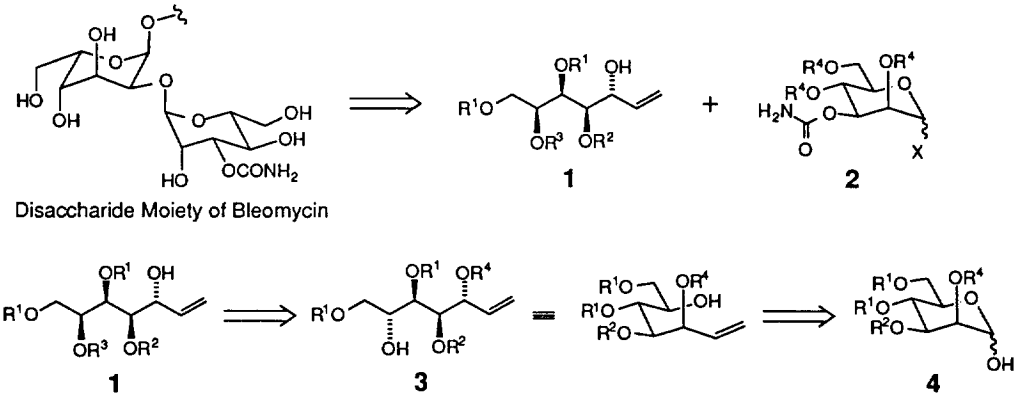
In previous communications we reported (1) a novel approach to L-gulose from D-mannose,[10] (2) a regioselective preparation of 3-*O*-carbamoyl-D-mannose,[11] and (3) an efficient coupling of each fragment and further transformation to the disaccharide moiety.[11] This paper describes in full detail the synthesis of 2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose.

Synthetic Strategy

Synthesis of the disaccharide moiety has been accomplished by three groups as a part of the total synthesis of BLM. In early work by Umezawa *et al.*[12] and Hecht *et al.*,[13] the L-gulose skeleton was constructed from D-glucose based on the consideration that the interconversion of the oxidation level of C1 and C6 of D-glucose would give L-gulose. Alternatively, we envisioned that inversion of the stereochemistry at C5 of D-mannose would also provide a novel approach to L-gulose. Indeed, independent of our work, Boger *et al.*[14] recently developed a stereoselective transformation of D-mannose to the L-gulose skeleton using a Rh(I)-catalyzed hydroboration of a 6-deoxy-hex-5-enopyranoside derivative during the course of their total synthesis of BLM.[14,15]

Our basic strategy is shown in Scheme 1. The key feature is that a linear allylic alcohol **1** was envisaged as an equivalent of L-gulose and was expected to be a potential glycosyl acceptor because the hydroxyl at C2[16] is a reactive allylic hydroxyl.[17] Heptose **1**, in turn, might be obtained from a suitably protected D-mannopyranose **4** by Wittig reaction, followed by inversion of stereochemistry at C5 of the resulting **3**. After glycosylation of **1** with mannose segment **2**, ozonolysis of the exomethylene part would afford the disaccharide moiety of BLM.

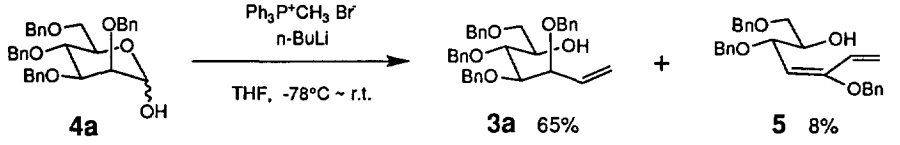
Scheme 1



Transformation of D-Mannose to L-Gulose

Transformation of D-mannose to L-gulose was first examined with 2,3,4,6-tetra-*O*-benzyl-D-mannose **4a** as a model. Treatment of **4a** in THF with 2 equivalents of ylide generated from phosphonium bromide and n-BuLi gave the heptenol **3a** in 65% yield along with the undesired dienol **5** in 8% yield (Scheme 2).

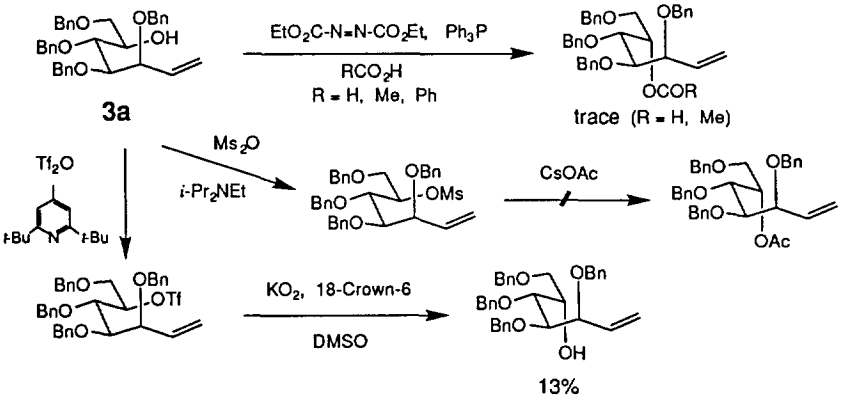
Scheme 2



In the case of the related D-glucose derivative, Sinaÿ *et al.*[18] reported that the formation of enol and/or dienol depends on the solvent and base employed. Indeed, when the ylide was generated using potassium hexamethyldisilazide (KHMDS) as a base, dienol **5** was obtained exclusively in 80% yield. Further, the yield of **3a** was improved to 87% by the pretreatment of **4a** with an equimolar amount of n-BuLi followed by the reaction with $Ph_3P{=}CH_2$ (base: n-BuLi).

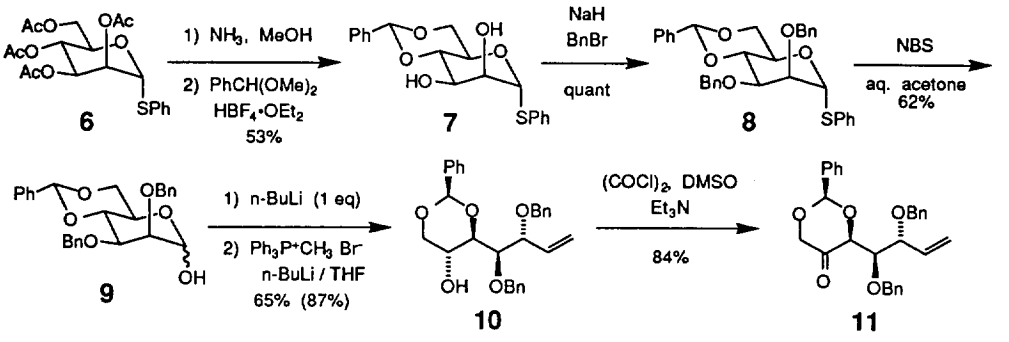
With heptose **3a** in hand, S_N2 type inversion at C5[16] was initially attempted. Various methods, such as the Mitsunobu reaction[19] or the substitution of sulfonates with CsOAc[20] or KO_2,[21] gave the inversion product only in low yields (Scheme 3).

Scheme 3



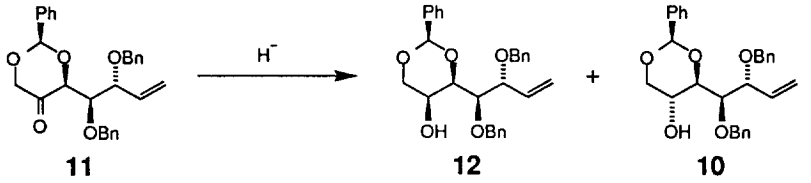
We then became interested in an alternative oxidation-reduction approach *via* a 5-keto derivative.[16] Protection of O-4 and O-6 as a benzylidene acetal was considered most suitable for achieving high stereoselectivity because the 5-keto group becomes part of a 6-membered dioxanone ring. In a model study, both hydroxyl groups in benzylidene thiomannoside **7**, prepared from **6** in 53% yield, were benzylated to provide fully protected thioglycoside **8** in 98% yield. Selective protection of O-2 or O-3 in **7** was also possible *via* its stannylene acetal, and that methodology was successfully utilized in the preparation of both the L-gulose and 3-*O*-carbamoyl-D-mannose segments (*vide infra*). Thioglycoside **8** was hydrolyzed with NBS in acetone-H_2O to afford hemiacetal **9**, and Wittig olefination of the latter proceeded smoothly giving the 5α-hydroxy-1,3-dioxane **10**[22] in 65% yield (87% conversion yield based on recovered **9**). Swern oxidation of dioxanol **10** gave the dioxanone **11** in 84% yield (Scheme 4).

Scheme 4



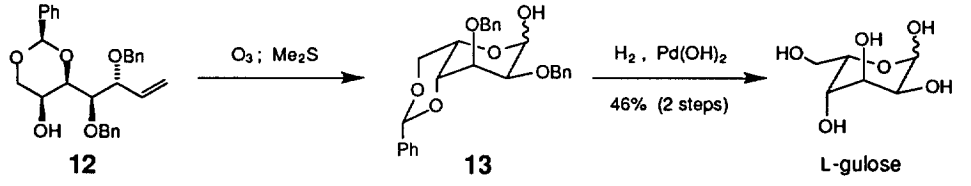
Dioxanone **11** was then subjected to reduction with various hydride reagents. As shown in Scheme 5, the desired β-alcohol **12** was exclusively formed when LiBH(*sec*-Bu)$_3$ (L-Selectride) was used. Brown *et al.* reported that the equatorial attack by L-Selectride was particularly significant in the case of α-substituted cyclohexanones.[23] The small coupling constants of H-5 ($J_{5,6eq}$=~0Hz, $J_{5,6ax}$=2.0Hz and $J_{4,5}$=1.1Hz) well supported the axial orientation of the hydroxyl group in **12**. On the other hand, preferential axial attack was observed with $NaBH_4$ and DIBAL. Conversion of the heptose **12** to L-gulose was accomplished in 46% overall yield by ozonolysis of the terminal olefin and hydrogenolysis of the benzylidene and benzyl groups (Scheme 6). In this way we have established a novel method for the conversion of D-mannose to L-gulose by inversion at C-5 through an oxidation-reduction sequence.[10]

Scheme 5



"H$^-$"-Source	Yield (%)	12 : 10
$NaBH_4$	96	22 : 78
DIBAL	92	23 : 77
LiBH(*sec*-Bu)$_3$	90	>99 : 1

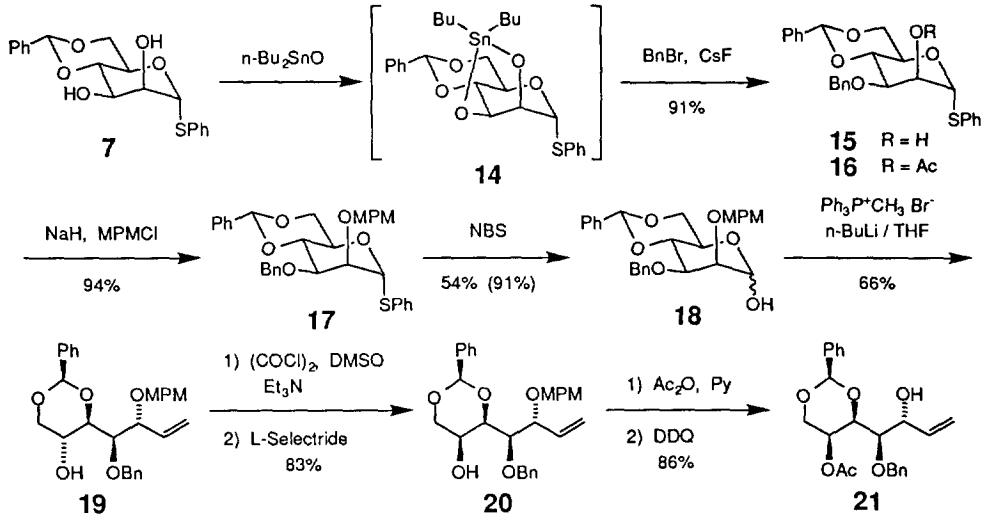
Scheme 6



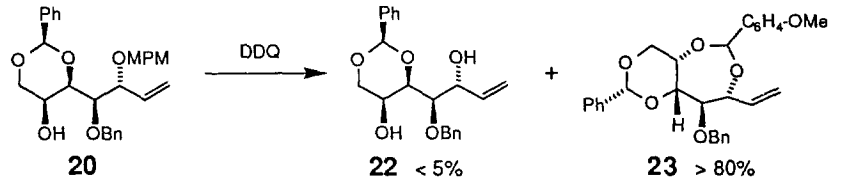
Preparation of L-Gulose Synthon

For the attachment of the D-mannose portion it was necessary to differentiate the gulose C2 hydroxyl. CsF-mediated regioselective alkylation of stannylene acetal **14**[24] was examined for this purpose. Boger *et al.*[14] had also utilized stannylene acetal methodology for the selective O-3 alkylation of the related mannose derivatives. Stannylene acetal **14**, prepared from diol **7**, was found to undergo regioselective benzylation at room temperature in the presence of CsF to afford O-3 benzylation product **15** as a single isomer. The structure of **15** was confirmed after acetylation to **16**. In the ^{1}H-NMR spectrum of acetate **16**, H-2 was shifted downfield; δ 4.29 (H-2; $J_{1,2}$=1.0, $J_{2,3}$=3.4 Hz) and δ 3.97 (H-3; $J_{2,3}$=3.4, $J_{3,4}$=9.5Hz) for **15**; δ 5.62 (H-2; $J_{1,2}$=1.4, $J_{2,3}$=3.4 Hz) and δ 3.86 (H-3; $J_{2,3}$=3.4, $J_{3,4}$=9.8 Hz) for **16**.

Scheme 7



Scheme 8

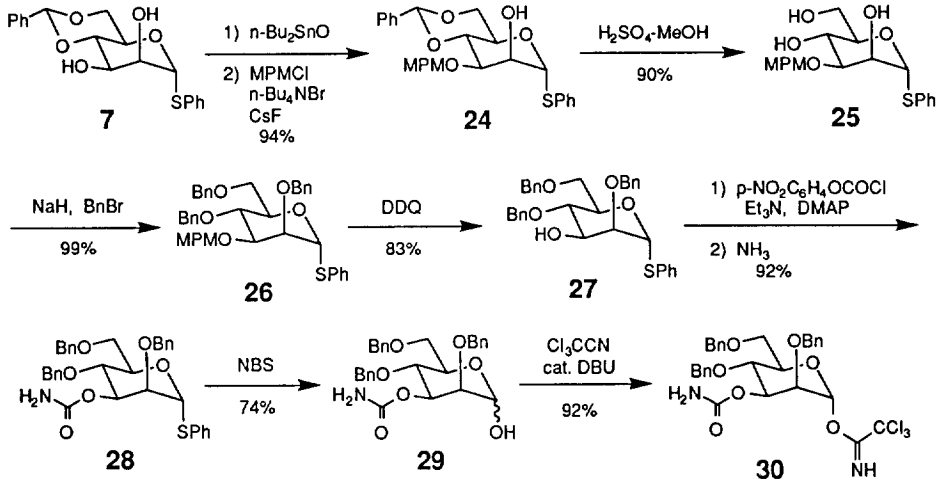


The remaining hydroxyl at C2 of **15** was protected as an MPM (4-methoxybenzyl) ether, and thioglycoside **17** was hydrolyzed to mannopyranose **18** in 54% yield (91% conversion yield based on recovered **17**). Methylenation of **18** was carried out using $Ph_3P{=}CH_2$ to obtain heptose **19** in 66% yield. Following the protocol established in the model study described above, D-manno-type **19** was converted to L-gulo-type **20** in 83% overall yield with complete stereoselectivity. After acetylation of dioxanol **20**, the MPM group was selectively deprotected[25] to obtain allylic alcohol **21** which serves as a glycosyl acceptor (Scheme 7). When dioxanol **20** was treated with DDQ, the desired diol **22** was obtained only in low yield, and the acetal **23** was isolated in high yield instead (Scheme 8). Therefore, the dioxanol hydroxyl was acetylated prior to the deprotection of the MPM group. Related oxidative acetalization was also reported by Yonemitsu *et al.*[26]

Preparation of 3-*O*-Carbamoyl-D-Mannose Portion

In the preparation of L-gulose synthon we described the regioselective benzylation at C3-OH of 4,6-*O*-benzylidene mannose **7** through its stannylene acetal. The same strategy was also applied for the preparation of the 3-*O*-carbamoyl-D-mannose moiety (Scheme 9). In this case 4-methoxybenzyl group (MPM) was introduced instead at O-3. Thus, the stannylene acetal **14** derived from **7** was reacted with MPMBr, prepared *in situ* from MPMCl and n-Bu_4NBr, in the presence of CsF to afford **24** in 94% yield as a single isomer. The regiochemistry of **24** was tentatively assigned in analogy to that of **15**, and was confirmed after transforming to the carbamoyl derivative **28**. The benzylidene group was hydrolyzed, and the resulting triol **25** was benzylated to obtain **26** almost quantitatively. Then the MPM group was selectively deprotected with DDQ to generate the C3-OH. The introduction of a carbamoyl group was carried out in 92% yield by a conventional method, *p*-nitrophenyl carbonation followed by ammonolysis. The 3-*O*-carbamoyl structure was confirmed by NMR. Thus, in the ^{1}H-NMR spectrum of carbamoyl mannoside **28**, H-3 and H-2 appeared at δ 5.13 (dd, $J_{2,3}$=3.2, $J_{3,4}$=9.2Hz) and δ 4.14 (dd, $J_{2,3}$=3.2, $J_{1,2}$=2.1Hz), respectively. Thioglycoside **28** was hydrolyzed with NBS, and the resulting **29** was reacted with Cl_3CCN and a catalytic amount of DBU to obtain **30** in 92% yield.[27] Trichloroacetimidate **30** serves as a glycosyl donor.

Scheme 9



Boger *et al.* also established an efficient route to 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl mannose (not shown) employing a similar stannylene acetal methodology.[14] Our approach, although it seems complementary to that of Boger *et al.*, is quite useful because the disaccharide moiety can be prepared in a differently protected manner.

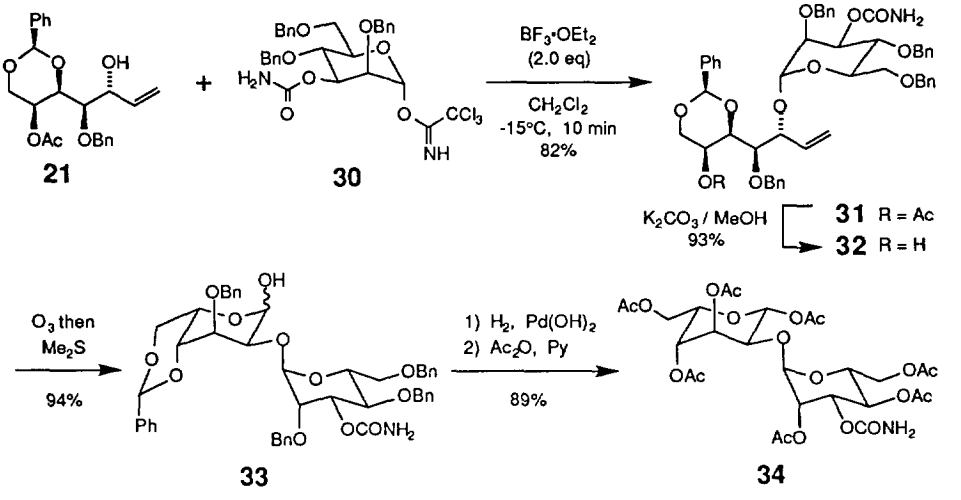
We were thus able to prepare both L-gulose and D-mannose segments from the common intermediate **7**, and the stannylene acetal methodology was successfully applied to achieve the regioselective alkylation of 4,6-*O*-benzylidene mannoside **7**.

Coupling of Two Segments and Synthesis of Disaccharide

With both glycosyl acceptor and donor in hand, the coupling of **21** and **30** was then examined. When allyl alcohol **21** was treated with trichloroacetimidate **30** in CH_2Cl_2 in the presence of BF_3•OEt_2, glycosylation

proceeded smoothly at -15°C within 10 min to isolate the desired α-mannosyl derivative **31** in 82% yield (Scheme 10). The high reactivity of **21** is noteworthy and is apparently derived by masking the C1 carbonyl as a vinyl group.

Scheme 10



After deacetylation, the resulting hydroxy olefin **32** was subjected to ozonolysis to obtain **33** as an anomeric mixture (α:β=*ca* 2:1). Hydrogenolysis using $Pd(OH)_2$ gave free 2-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulose, which was converted to the heptaacetate **34** in 89% yield as a single β-anomer ($J_{1,2}$=8.4 Hz). Spectral data (^{1}H-and ^{13}C-NMR) of **34** were identical to those kindly provided by Prof. D. L. Boger (The Scripps Research Institute). Selective deprotection of the anomeric acetate in **34** has already been established by Boger *et al.*[14]

In conclusion, we have developed a new route to the disaccharide moiety of BLM. The key features of the present synthesis are as follows: (1) the L-gulose skeleton is stereoselectively constructed from D-mannose by inversion of stereochemistry at C5 through an oxidation-reduction sequence; (2) methylenation of the C1 carbonyl group of **4** not only served as temporary protection but also resulted in increased nucleophilicity of the C2 hydroxyl group; (3) stannylene acetal methodology was effectively applied for the preparation of both fragments. Further, it should also be emphasized that both **33** and **34** are considered versatile intermediates for introducing the disaccharide moiety into diverse types of compounds. Protecting groups in **33** (Bn) and **34** (Ac) may be removed under quite different conditions after introduction of a given aglycon. Since the disaccharide moiety of BLM is hypothesized to play a central role in molecular recognition at cell surfaces and also in cell permeability, the biological properties of such hybrid compounds bearing the disaccharide are likely to prove quite interesting. Synthetic efforts along these lines are now in progress.

Experimental Section

All melting points were determined with a Yanagimoto MP-21 melting point apparatus and were uncorrected. Optical rotations were measured with a Horiba SEPA-200 auto digital polarimeter. Infrared (IR) spectra were recorded on a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured with a Bruker AC 200P (200MHz), and a Bruker AM 400 (400MHz) spectrometer. The chemical shifts are expressed in ppm down-field from tetramethylsilane, using tetramethylsilane (δ=0) and/or residual chloroform (δ=7.25) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Elemental analysis was performed with Perkin-Elmer 240 or 2400. Mass spectra were taken with a Hitachi M-80A or M-80B mass spectrometer. Unless otherwise noted, all experiments were carried out under an atmosphere of dry argon using anhydrous solvents. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254, 0.25mm, Art 5715) were used. The following abbreviations were used for solvents: tetrahydrofuran (THF), diethyl ether (Et_2O), ethyl acetate (AcOEt), methanol (MeOH), and dichloromethane (CH_2Cl_2).

(2*R*,3*R*,4*R*,5*R*)-1,3,4,5-Tetrabenzyloxy-6-hepten-2-ol (3a): To a solution of **4a** (1.215 g, 2.25 mmol) in THF (10 mL) was added a 1.6 *M* hexane solution of n-BuLi (1.45 mL, 2.33 mmol) at -78°C. The mixture was stirred at 0°C for 5 min and then cooled to -78°C. To the above solution was added the THF solution (10 mL) of $Ph_3P{=}CH_2$, prepared from $Ph_3PCH_3{}^+Br^-$ (0.889 g, 2.49 mmol) and n-BuLi (1.6*M* hexane solution, 1.70 mL, 2.73 mmol), and the mixture was stirred at r.t. for 30 hr. The reaction mixture was poured into sat. $NaHCO_3$, and the products were extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane=1/9) to give **3a** (1.06 g, 87%) as a colorless oil. $[\alpha]_D^{20}$ +7.2° (*c* 1.00, $CHCl_3$): IR (neat) 3030, 2912, 2866, 1496, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.64 (1H, d, *J*=4.8Hz, OH), 3.63 (1H, dd, *J*=3.2, 9.8Hz), 3.66 (1H, dd, *J*=5.5, 9.8Hz), 3.84-3.89 (2H, m), 4.00 (1H, m), 4.11 (1H, m), 4.24 (1H, d, *J*=11.5Hz), 4.44-4.65 (7H, m), 4.71 (1H, d, *J*=11.0Hz), 5.40 (1H, dd, *J*=1.5, 10.1Hz), 5.44 (1H, dd, *J*=1.1, 17.4Hz), 5.96 (1H, ddd, *J*=8.0, 10.1, 17.4Hz), 7.20-7.30 (20H, m): EI-MS *m/z* 539 ([M+1]$^+$).

Phenyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (7): **6** (6.41 g, 14.6 mmol) was dissolved in MeOH (70 mL) saturated with NH_3. The mixture was stirred at r.t. overnight, and the removal of the solvent gave the crude phenyl 1-thio-α-D-mannopyranoside. The crude material was dissolved in DMF (20 mL), and to the mixture was added successively benzaldehyde dimethylacetal (2.18 mL, 14.5 mmol) and $HBF_4{\cdot}OEt_2$ (85% Et_2O solution, 1.68 mL, 11.4 mmol) at 0°C. After being stirred at r.t. overnight, Et_3N (2.5 mL) was added, and the mixture was poured into H_2O (150 mL). The precipitate was filtered, washed with cold Et_2O, and dried under vacuum to give **7** (2.79 g, 53%) as white crystals. m.p. 213-214°C (AcOEt): $[\alpha]_D^{20}$ +289° (*c* 0.50, $CHCl_3$/MeOH=1/1): IR (KBr) 3346, 1452cm^{-1}: ^{1}H-NMR (200MHz, $CDCl_3/CD_3OD$= 10/1) δ 3.85 (1H, t, *J*=10.1Hz), 3.96-4.12 (2H, m), 4.17-4.40 (3H, m), 5.57 (1H, d, *J*=0.9 Hz,), 5.59 (1H, s), 7.25-7.55 (10H, m).

Phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (8): DMF solution (50 mL) of **7** (8.00 g, 22.2 mol) was added to a suspension of NaH (*ca* 60% in mineral oil, 2.36 g, 59.1 mmol) in DMF (30 mL) at 0°C, and the mixture was stirred for 30 min. To the mixture was added benzyl bromide (7.14 mL, 59.9 mmol), and the reaction mixture was stirred at r.t. for 8 hr. MeOH (6 mL) was added and the mixture was poured into H_2O. The products were extracted with Et_2O, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane=1/9) to give **8** (11.8 g, 98%) as white crystals. m.p. 84-85°C (AcOEt/Et_2O): $[\alpha]_D^{20}$ +107° (*c* 1.13, $CHCl_3$): IR (KBr) 3034, 2895, 2864, 1581, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.89 (1H, t, *J*=9.5Hz), 3.97 (1H, dd, *J*=3.2, 9.5Hz), 4.04 (1H, dd, *J*=1.4, 3.2Hz), 4.20-4.35 (3H, m), 4.66 (1H, d, *J*=12.2Hz), 4.73 (2H, br.s), 4.83 (1H, d, *J*=12.2Hz), 5.51 (1H, d, *J*=1.4Hz), 5.65 (1H, s), 7.25-7.41 (18H, m), 7.52 (2H, m): *Anal.* Calcd for $C_{33}H_{32}O_5S$: C, 73.31; H, 5.97; S, 5.93%. Found: C, 73.33; H, 6.06; S, 5.92%.

2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranose (9): **8** (11.3 g, 20.9 mmol) was dissolved in acetone-H_2O (24/1, 80 mL), and was added dropwise a acetone-H_2O (24/1, 80 mL) solution of NBS (22.2 g, 125 mmol) at 0°C. The mixture was stirred at r.t. for 25 min, and the reaction was quenched with sat. Na_2SO_3. The products were extracted with Et_2O, and the organic layer was successively washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **9** (5.80 g, 62%) as an anomeric mixture. ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.65 (1H, d, *J*=3.4 Hz, OH), 3.86 (1H, dd, *J*=1.6, 3.1Hz), 3.86 (1H, t, *J*=10.1Hz), 4.02 (1H, dd, *J*=3.1, 9.8Hz), 4.02 (1H, ddd, *J*=4.6, 9.8, 10.1Hz), 4.23 (1H, dd, *J*=4.6, 10.1Hz), 4.26 (1H, t, *J*=9.8Hz), 4.67 (1H, d, *J*=12.2Hz), 4.73 (1H, d, *J*=12.2Hz), 4.83 (1H, d, *J*=12.2Hz), 4.84 (1H, d, *J*=12.2Hz), 5.19 (1H, dd, *J*=1.6, 3.4Hz), 5.64 (1H, s), 7.26-7.41 (18H, m), 7.50 (2H, m): *Anal.* Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29%. Found: C, 72.10; H, 6.51%.

(1'*R*,2*R*,2'*R*,4*R*,5*R*)-4-(1,2-Dibenzyloxy-3-butenyl)-2-phenyl-1,3-dioxan-5-ol (10): **9** (1.63 g, 3.62 mmol) was reacted with $Ph_3P{=}CH_2$ in a manner similar to the preparation of **3a** to give **10** (1.06 g, 65%, and 87% conversion yield based on recovered **9** (0.40 g)) as white crystals. m.p. 85°C (Et_2O/hexane): $[\alpha]_D^{20}$ -48.2° (*c* 1.04, $CHCl_3$): IR (KBr) 3476, 2903, 2870, 1643, 1452cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.70 (1H, d, *J*=4.0Hz, OH), 3.52 (1H, dd, *J*=9.3, 9.4Hz), 3.84-3.94 (3H, m), 4.22 (1H, dd, *J*=4.8, 10.4Hz), 4.23 (1H, dd, *J*=6.8, 7.4Hz), 4.38 (1H, d, *J*=11.7Hz), 4.59 (1H, d, *J*=11.7Hz), 4.66 (1H, d, *J*=11.7Hz), 4.79 (1H, d, *J*=11.7Hz), 5.37 (1H, s), 5.44 (1H, ddd, *J*=0.6, 1.6, 10.3Hz), 5.47 (1H, ddd, *J*=0.7, 1.6, 17.7Hz), 6.05 (1H, ddd, *J*=7.6, 10.3, 17.7Hz), 7.23-7.40 (15H, m): *Anal.* Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77%. Found: C, 75.40; H, 6.82%.

(1'*R*,2*R*,2'*R*,4*R*)-4-(1,2-Dibenzyloxy-3-butenyl)-2-phenyl-1,3-dioxan-5-one (11): DMSO (0.28 mL, 3.95 mmol) was added to a CH_2Cl_2 solution (1.5 mL) of oxalyl chloride (0.17 mL, 1.95 mmol) at -50°C, and the mixture was stirred at that temperature for 15 min. Then **10** (369.7 mg, 0.83 mmol) in CH_2Cl_2 (1.5 mL) was added at -50°C. After being stirred at -50°C for 30 min and at -18°C for 10 min, Et_3N (1.20 mL, 8.61 mmol) was added at -18°C. After being stirred at -18°C for 10 min and at 0°C for 10 min, the reaction mixture was poured into sat. $NaHCO_3$. The products were extracted with Et_2O, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **11** (309.2 mg, 84%) as a syrup. ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.13 (1H, dd, *J*=2.0, 8.9Hz), 4.18 (1H, dd, *J*=7.2, 8.9Hz), 4.35 (1H, d, *J*=11.7Hz), 4.42 (2H, d, *J*=11.0Hz), 4.51 (1H, d, *J*=11.0Hz), 4.62 (1H, d, *J*=11.0Hz), 4.63 (1H, d, *J*=11.7Hz), 4.91 (1H, d, *J*=2.0Hz), 5.41 (1H, d, *J*=10.3Hz), 5.46 (1H, d, *J*=17.4Hz), 5.85 (1H, s), 5.91 (1H, ddd, *J*=7.2, 10.3, 17.4Hz), 7.20-7.49 (15H, m).

(1'*R*,2*R*,2'*R*,4*R*,5*S*)-4-(1,2-Dibenzyloxy-3-butenyl)-2-phenyl-1,3-dioxan-5-ol (12): A THF solution of L-Selectride (1.0 *M*, 1.0 mL, 1.0 mmol) was added to a THF solution (4 mL) of **11** (309.2 mg, 0.69 mmol) at -78°C. The mixture was stirred at -78°C for 90 min, then at 0°C for 30 min. The reaction was quenched with brine, and the products were extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **12** (279.5 mg, 90%) as white crystals. m.p. 101-102°C (Et_2O/hexane): $[\alpha]_D^{20}$ -30.6° (*c* 0.98, $CHCl_3$): IR (KBr) 3485, 2914, 2872, 1496, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.13 (1H, d, *J*=9.6Hz, OH), 3.65 (1H, dddd, *J*=1.1, 1.4, 2.0, 9.6Hz), 3.98 (1H, dd, *J*=4.2, 7.3Hz), 4.00 (1H, dd, *J*=1.4, 11.9Hz), 4.03 (1H, dd, *J*=1.1, 7.3Hz), 4.12 (1H, dd, *J*=4.2, 8.1Hz), 4.18 (1H, dd, *J*=2.0, 11.9Hz), 4.43 (1H, d, *J*=11.8Hz), 4.66 (1H, d, *J*=11.8Hz), 4.75 (1H, d, *J*=11.0Hz), 4.80 (1H, d, *J*=11.0Hz), 5.35 (1H, ddd, *J*=0.9, 1.7, 17.3Hz), 5.40 (1H, ddd, *J*=0.6, 1.7, 10.3Hz), 5.57 (1H, s), 6.04 (1H, ddd, *J*=8.1, 10.3, 17.3Hz), 7.23-7.40 (13H, m), 7.50 (2H, m): *Anal.* Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77%. Found: C, 75.33; H, 6.75%.

Transformation of 12 to L-Gulose: Ozone gas was passed into a MeOH solution (10 mL) of **12** (194.5 mg, 0.44 mmol) at -78°C for 40 min until the solution became blue. Ar gas was then passed into the solution to remove an excess ozone. Me_2S (0.30 mL) was added to the reaction mixture, and the mixture was allowed to warm to r.t.. The mixture was concentrated under reduced pressure, and the residue was

chromatographed on silica gel (AcOEt/hexane) to give **13** (168.5 mg, 86%) as an anomeric mixture. A mixture of **13** (15.2 mg, 0.03 mmol) and 20% $Pd(OH)_2$ (15 mg) in MeOH (10 mL) was stirred under H_2 (20 atm) in a sealed tube for 3 hr. The catalyst was filtered off, and the removal of the solvent gave L-gulose (3.1 mg, 56%) as a solid. ^{1}H-NMR (400MHz, CD_3OD) δ 3.56 (1H, dd, *J*=3.3, 8.2Hz), 3.68 (1H, dd, *J*=5.5, 11.3Hz), 3.71 (1H, m), 3.73 (1H, dd, *J*=6.5, 11.3Hz), 3.92 (1H, ddd, *J*=1.0, 5.5, 6.5Hz), 3.95 (1H, t, *J*=3.3Hz), 4.80 (1H, d, *J*=8.2Hz).

Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (15): A mixture of **7** (0.859 g, 2.38 mmol) and Bu_2SnO (0.605 g, 2.43 mmol) in toluene (30 mL) was heated under refluxing for 3 hr. The solvent was removed under reduced pressure to obtain crude **14**. The mixture of crude **14**, CsF (0.369 g, 2.43 mmol) and benzyl bromide (0.29 mL, 2.44 mmol) in DMF (10 mL) was stirred at r.t. for 12 hr. The reaction mixture was poured into sat. $NaHCO_3$, and the products were extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **15** (0.981 g, 91%) as white crystals. m.p. 89-90°C (Et_2O/hexane): $[\alpha]_D^{20}$ +228° (*c* 1.07, $CHCl_3$): IR (KBr) 3454, 2899, 1736cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.83 (1H, d, J=1.3Hz, OH), 3.86 (1H, t, *J*=10.3Hz), 3.97 (H, dd, *J*=3.4, 9.5Hz), 4.18 (1H, t, *J*=9.5Hz), 4.21 (1H, dd, *J*=4.9, 10.3Hz), 4.29 (1H, ddd, *J*=1.0, 1.3, 3.4Hz), 4.34 (1H, ddd, *J*=4.9, 9.5, 10.3Hz), 4.75 (1H, d, *J*=11.8Hz), 4.90 (1H, d, *J*=11.8Hz), 5.60 (1H, d, *J*=1.0Hz), 5.63 (1H, s), 7.28-7.53 (15H, m): *Anal.* Calcd for $C_{26}H_{26}O_5S$: C, 69.31; H, 5.82; S, 7.12%. Found: C, 69.07; H, 5.90; S, 6.83%.

Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(4-methoxybenzyl)-1-thio-α-D-mannopyranoside (17): A DMF solution (9 mL) of **15** (0.853 g, 1.89 mmol) was added to a suspension of NaH (*ca* 60% in mineral oil, 83.5 mg, 2.09 mmol) in DMF (1 mL) at 0°C. After being stirred at 0°C, the mixture was added MPMCl (0.29 mL, 2.06 mmol), and was stirred at r.t. for 12 hr. MeOH and H_2O (30 mL) was added, and the products were extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **17** (1.019 g, 94%) as a syrup. $[\alpha]_D^{20}$ +112° (*c* 0.66, $CHCl_3$): IR (neat) 3063, 2901, 2864, 1612cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.79 (3H, s), 3.88 (1H, dd, *J*=9.5, 9.5Hz), 3.95 (1H, dd, *J*=3.2, 9.5Hz), 4.02 (1H, dd, *J*=1.4, 3.2Hz), 4.19-4.32 (3H, m), 4.64 (1H, d, *J*=12.1Hz), 4.65 (2H, br.s), 4.81 (1H, d, *J*=12.1Hz), 5.46 (1H, d, *J*=1.4Hz), 5.64 (1H, s), 6.84 (2H, m), 7.25-7.40 (15H, m), 7.52 (2H, m): *Anal.* Calcd for $C_{34}H_{34}O_6S$: C, 71.56; H, 6.01; S, 5.62%. Found: C, 71.28; H, 6.05; S, 5.47%.

3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(4-methoxybenzyl)-D-mannopyranose (18): NBS (127.3 mg, 0.72 mmol) was added to **17** (388.6 mg, 0.68 mmol) in acetone(15 mL) containing H_2O (0.3 mL) at 0°C, and the mixture was stirred at r.t. for 30 min. The reaction was quenched with sat. Na_2SO_3, and the products were extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **18** (175.0 mg, 54%, and 91% conversion yield based on recovered **17** (158.2 mg)) as an anomeric mixture. ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.66 (1H, d, *J*=3.5Hz, OH), 3.78 (3H, s), 3.84 (1H, dd, *J*=1.6, 3.1Hz), 3.85 (1H, t, *J*=10.2Hz), 4.00 (1H, dd, *J*=3.1, 9.8Hz), 4.02 (1H, ddd, *J*=3.1, 4.8, 9.7Hz), 4.22 (1H, dd, *J*=4.8, 10.2Hz), 4.24 (1H, dd, *J*=9.7, 9.8Hz), 4.65 (1H, d, *J*=12.2Hz), 4.66 (1H, d, *J*=12.0Hz), 4.76 (1H, d, *J*=12.0Hz), 4.83 (1H, d, *J*=12.2Hz), 5.14 (1H, dd, *J*=1.6, 3.5Hz), 5.64 (1H, s), 6.85 (2H, m), 7.24-7.52 (12H, m).

(1'*R*,2*R*,2'*R*,4*R*,5*R*)-4-[(1-Benzyloxy-2-(4-methoxybenzyl)oxy-3-butenyl]-5-hydroxy-2-phenyl-1,3-dioxane (19): **18** (6.90 g, 14.4 mmol) was reacted with $Ph_3P{=}CH_2$ in a manner similar to the preparation of **3a** to give **19** (4.56 g, 66%) as white crystals. m.p. 100-102°C (Et_2O/hexane): $[\alpha]_D^{20}$ -56.2° (*c* 1.35, $CHCl_3$): IR (KBr) 3437, 2932, 2866, 1612cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.71 (1H, d, *J*=4.0 Hz, OH), 3.51 (1H, dd, *J*=9.5, 10.8Hz), 3.72 (3H, s), 3.80-3.90 (3H, m), 4.22 (1H, dd, *J*=4.8, 10.4Hz), 4.23 (1H, dd, *J*=6.8, 7.7Hz), 4.31 (1H, d, *J*=11.4Hz), 4.58 (1H, d, *J*=11.7Hz), 4.59 (1H, d, *J*=11.4Hz), 4.76 (1H, d, *J*=11.7Hz), 5.35 (1H, s), 5.44 (1H, dd, *J*=1.7, 9.8Hz), 5.47 (1H, dd, *J*=1.7, 17.4Hz), 6.03 (1H, ddd, *J*=7.6, 9.8, 17.4Hz), 6.79 (2H, m), 7.22 (2H, m), 7.31-7.39 (10H, m): *Anal.* Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77%. Found: C, 73.02; H, 6.83%.

(1'*R*,2*R*,2'*R*,4*R*,5*S*)-4-[(1-Benzyloxy-2-(4-methoxybenzyl)oxy-3-butenyl]-5-hydroxy-2-phenyl-1,3-dioxane (20): **19** (2.33 g, 4.90 mmol) was oxidized with oxalyl chloride (0.94 mL, 11 mmol), DMSO (1.53 mL, 22 mmol) and Et_3N (3.41 mL, 24.5 mmol) in CH_2Cl_2 (55 mL) in a manner similar to the preparation of **11**. Resulting crude dioxanone (2.32 g) was reduced with L-Selectride (1.0 *M* THF solution, 7.34 mL, 7.34 mmol) in a manner similar to the preparation of **12** to give **20** (1.94 g, 83% from **19**) as white crystals. m.p. 109-110°C (Et_2O/hexane): $[\alpha]_D^{20}$ -33.8° (*c* 0.88, $CHCl_3$): IR (KBr) 3489, 2905, 2068, 1614, 1518, 1452cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.17 (1H, d, *J*=9.6Hz, OH), 3.65 (1H, dddd, *J*=1.1, 1.4, 2.0, 9.6Hz), 3.79 (3H, s), 3.93 (1H, dd, *J*=4.6, 7.1Hz), 4.00 (1H, dd, *J*=1.4, 11.9 Hz), 4.03 (1H, dd, *J*=1.1, 7.1Hz), 4.10 (1H, dd, *J*=4.6, 8.0Hz), 4.19 (1H, dd, *J*=2.0, 11.9Hz), 4.36 (1H, d, *J*=11.6Hz), 4.59 (1H, d, *J*=11.6Hz), 4.73 (1H, d, *J*=11.0Hz), 4.77 (1H, d, *J*=11.0Hz), 5.34 (1H, ddd, *J*=0.8, 1.7, 17.3Hz), 5.40 (1H, dd, *J*=0.6, 1.7, 10.3Hz), 5.57 (1H, s), 6.03 (1H, ddd, *J*=8.0, 10.3, 17.3 Hz), 6.85 (2H, m), 7.25-7.38 (10H, m), 7.56 (2H, m): *Anal.* Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77%. Found: C, 73.06; H, 6.88%.

(1'*R*,2*R*,2'*R*,4*R*,5*S*)-5-Acetoxy-4-[1-benzyloxy-2-(4-methoxybenzyl)oxy-3-butenyl]-2-phenyl-1,3-dioxane: A mixture of **20** (153.5 mg, 0.322 mmol), Ac_2O (0.5 mL) and pyridine (2 mL) was stirred at r.t. for 6 hr. The reaction mixture was diluted with Et_2O (30 mL), washed successively with sat. $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The Et_2O solution was concentrated under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/hexane) to give (1'*R*,2*R*,2'*R*,4*R*,5*S*)-5-acetoxy-4-[1-benzyloxy-2-(4-methoxybenzyl)oxy-3-butenyl]-2-phenyl-1,3-dioxane (157.5 mg, 94%) as a colorless oil. $[\alpha]_D^{20}$ -6.87° (*c* 1.25, $CHCl_3$): IR (neat) 2914, 2866, 1738, 1612, 1514, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.99 (3H, s), 3.79 (1H, dd, *J*=3.1, 8.1Hz), 3.80 (3H, s), 3.95 (1H, dd, *J*=3.1, 8.4Hz), 4.00 (1H, dd, *J*=1.6, 13.0Hz), 4.07 (1H, dd, *J*=1.6, 8.4Hz), 4.28 (1H, dd, *J*=1.6, 13.0Hz), 4.31 (1H, d, *J*=11.8Hz), 4.57 (1H, d, *J*=11.8Hz), 4.72 (1H, q, *J*=1.6Hz), 4.79 (1H, d, *J*=11.3Hz), 4.82 (1H, d, *J*=11.3Hz), 5.30 (1H, ddd, *J*=0.8, 1.5, 17.4Hz), 5.37 (1H, ddd, *J*=0.6, 1.5, 10.3Hz), 5.59 (1H, s), 5.96 (1H, ddd, *J*=8.1, 10.4, 17.4Hz), 6.87 (2H, m), 7.21-7.40 (10H, m), 7.51 (2H, m): *Anal.* Calcd for $C_{31}H_{34}O_7$: C, 71.80; H, 6.61%. Found: C, 71.70; H, 6.78%.

(1'*R*,2*R*,2'*R*,4*R*,5*S*)-5-Acetoxy-4-(1-benzyloxy-2-hydroxy-3-butenyl)-2-phenyl-1,3-dioxane (21): To a solution of (1'*R*,2*R*,2'*R*,4*S*,5*S*)-5-acetoxy-4-[1-benzyloxy-2-(4-methoxybenzyl)oxy-3-butenyl]-2-phenyl-1,3-dioxane (593 mg, 1.14 mmol) in CH_2Cl_2-H_2O (19/1, 6.3 mL) was added DDQ (286 mg, 1.26 mmol) at 0°C, and the reaction mixture was stirred at r.t. for 2.5 hr. The reaction mixture was diluted with CH_2Cl_2 (30 mL), and the insoluble material was filtered off. Filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/hexane) to give **21** (416 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ +22.5° (*c* 1.12, $CHCl_3$): IR (neat) 3452, 3034, 2862, 1738, 1496, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.18 (3H, s), 2.36 (1H, br, OH), 3.93 (1H, dd, *J*=3.7, 8.4Hz), 4.04 (1H, dd, *J*=1.6, 13.1Hz), 4.09 (1H, m), 4.12 (1H, dd, *J*=1.6, 8.4Hz), 4.31 (1H, dd, *J*=1.6, 13.1Hz), 4.69 (1H, d, *J*=11.3 Hz), 4.80 (1H, q, *J*=1.6Hz), 4.95 (1H, d, *J*=11.3Hz), 5.26 (1H, ddd, *J*=1.1, 1.2, 10.4Hz), 5.35 (1H, td, *J*=1.2, 17.3Hz), 5.63 (1H, s), 5.97 (1H, ddd, *J*=7.2, 10.4, 17.3Hz), 7.27-7.41 (8H, m), 7.52 (2H, m): *Anal.* Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58%. Found: C, 69.09; H, 6.54%.

Phenyl 4,6-*O*-benzylidene-3-*O*-(4-methoxybenzyl)-1-thio-α-D-mannopyranoside (24): **7** (3.17 g, 8.80 mmol) was converted to **14**, and **14** was reacted with CsF (1.36 g, 8.96 mmol) and MPMBr (1.85 g, 9.22 mmol) to give **24** (3.71 g, 88%) as white crystals. m.p. 100-101°C (Et_2O/hexane): $[\alpha]_D^{20}$ +209° (*c* 1.28, $CHCl_3$): IR (KBr) 3524, 2953, 2934, 2901, 2856, 1614, 1516, 1452, 1439cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.82 (1H, d, *J*=1.3 Hz, OH), 3.82 (3H, s), 3.85 (1H, t, *J*=10.3Hz), 3.95 (H, dd, *J*=3.4, 9.5Hz), 4.15 (1H, t, *J*=9.5Hz), 4.20 (1H, dd, *J*=4.9, 10.3Hz), 4.25 (1H, ddd, *J*=1.2, 1.3, 3.4Hz), 4.33 (1H, ddd, *J*=4.9, 9.5, 10.3Hz), 4.68 (1H, d, *J*=11.4Hz), 4.82 (1H, d, *J*=11.4Hz), 5.59 (1H, d, *J*=1.2Hz), 5.62 (1H, s), 6.89 (2H, m), 7.26-7.54 (12H, m): *Anal.* Calcd for $C_{27}H_{28}O_6S$: C, 67.48; H, 5.87; S, 6.67%. Found: C, 67.49; H, 5.99; S, 6.68%.

Phenyl 3-*O*-(4-methoxybenzyl)-1-thio-α-D-mannopyranoside (25): **24** (4.37 g, 9.09 mmol) was dissolved in MeOH (40 mL) containing 1% conc. H_2SO_4, and the mixture was stirred at 0°C for 30 min.

MeOH (40 mL) saturated with NH_3 was added, and the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel ($MeOH/CH_2Cl_2$) to give **25** (3.22 g, 90%) as white crystals. $[\alpha]_D^{20}$ +164° (*c* 1.04, $CHCl_3$): IR (KBr) 3418, 2910, 1614, 1514cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3/D_2O$) δ 3.65 (1H, dd, *J*=3.0, 9.2Hz), 3.68 (1H, dd, *J*=2.0, 12.3Hz), 3.80 (3H, s), 3.81 (1H, m), 4.00-4.08 (2H, m), 4.11 (1H, dd, *J*=1.5, 3.0Hz), 4.54 (1H, d, *J*=11.2Hz), 4.62 (1H, d, *J*=11.2 Hz), 5.50 (1H, d, *J*=1.5Hz), 6.89 (2H, m), 7.25-7.43 (7H, m): *Anal.* Calcd for $C_{20}H_{24}O_6S$: C, 61.21; H, 6.16; S, 8.17%. Found: C, 61.18; H, 6.19; S, 8.07%.

Phenyl 2,4,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-1-thio-α-D-mannopyranoside (26): **25** (3.04 g, 7.75 mmol) was benzylated in a manner similar to the preparation of **8** to give **26** (5.10 g, 99%) as a syrup. $[\alpha]_D^{20}$ +81.1° (*c* 1.21, $CHCl_3$): IR (neat) 3063, 3030, 2908, 2866, 1612, 1585, 1514, 1496, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.75 (1H, dd, *J*=1.8, 10.9Hz), 3.81 (3H, s), 3.81-3.87 (2H, m), 3.96 (1H, dd, *J*=1.7, 3.0Hz), 4.04 (1H, t, *J*=9.5Hz), 4.27 (1H, ddd, *J*=1.8, 5.0, 9.5Hz), 4.48 (1H, d, *J*=12.0Hz), 4.51-4.57 (3H, m), 4.64 (2H, m), 4.72 (1H, d, *J*=12.3Hz), 4.90 (1H, d, *J*=10.8Hz), 7.64 (2H, m), 7.18-7.46 (18H, m): *Anal.* Calcd for $C_{41}H_{42}O_6S$: C, 74.29; H, 6.39; S, 4.84%. Found: C, 74.32; H, 6.60; S, 4.87%.

Phenyl 2,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (27): **26** (5.10 g, 7.70 mmol) was reacted with DDQ (2.10 g, 9.24 mmol) in a manner similar to the preparation of **21** to give **27** (3.47 g, 83%) as syrup. $[\alpha]_D^{20}$ +117° (*c* 1.08, $CHCl_3$): IR (neat) 3431, 3063, 3030, 2916, 2866, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3/D_2O$) δ 3.74 (1H, dd, *J*=1.9, 10.9Hz), 3.77-3.88 (3H, m), 3.96-4.03 (2H, m), 4.29 (1H, ddd, *J*=1.9, 4.8, 9.7Hz),4.49 (1H, d, *J*=11.6Hz), 4.52 (1H, d, *J*=11.9Hz), 4.55 (1H, d, *J*=11.0Hz), 4.65 (1H, d, *J*=11.9Hz), 4.76 (1H, d, *J*=11.6Hz), 4.87 (1H, d, *J*=11.0Hz), 5.68 (1H, d, *J*=0.8Hz), 7.24-7.50 (20H, m).

Phenyl 2,4,6-tri-*O*-benzyl-3-*O*-carbamoyl-1-thio-α-D-mannopyranoside (28): Et_3N (2.88 mL, 20.7 mmol) was added to a mixture of **27** (4.48 g, 8.25 mmol) and 4-nitrophenyl chloroformate (3.83 g, 19.0 mmol) in THF (40 mL) at 0°C, and the mixture was stirred at r.t. for 6 hr. NH_3 gas was passed into the reaction mixture at 0°C for 1 hr, and the mixture was poured into sat. $NaHCO_3$. The products were extracted with AcOEt, and the organic layer was successively washed with 1*N* NaOH, brine, 1*N* HCl and brine, and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **28** (4.42 g, 92%) as a syrup. $[\alpha]_D^{20}$ +79.5° (*c* 1.04, $CHCl_3$): IR (neat) 3493, 3381, 2868, 1730, 1585, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3/D_2O$) δ 3.72 (1H, dd, *J*=1.9, 11.0 Hz), 3.84 (1H, dd, *J*=4.6, 11.0Hz), 4.08 (1H, dd, *J*=9.2, 9.5Hz), 4.14 (1H, dd, *J*=2.1, 3.2Hz), 4.33 (1H, ddd, *J*=1.9, 4.6, 9.5Hz), 4.48 (1H, d, *J*=12.0Hz), 4.51 (1H, d, *J*=12.4Hz), 4.56 (1H, d, *J*=12.0Hz), 4.64-4.72 (5H, m), 5.13 (1H, dd, *J*=3.2, 9.2Hz), 5.58 (1H, d, *J*=2.1Hz), 7.21-7.49 (20H, m): *Anal.* Calcd for $C_{34}H_{35}NO_6S$: C, 69.72; H, 6.02; N, 2.39; S, 5.47%. Found: C, 69.50; H, 6.03; N, 2.44; S, 5.59%.

2,4,6-Tri-*O*-benzyl-3-*O*-carbamoyl-D-mannopyranose (29): **28** (4.26 g, 7.27 mmol) was reacted with NBS (2.59 g, 14.5 mmol) in a manner similar to the preparation of **18** to give **29** (2.67 g, 74%) as an anomeric mixture. SI-MS (3-NBA, KCl) *m/z* 533 ($[M+1+K]^+$): *Anal.* Calcd for $C_{28}H_{31}NO_7$: C, 68.14; H, 6.33; N, 2.84%. Found: C, 67.87; H, 6.27; N, 2.73%.

2,4,6-Tri-*O*-benzyl-3-*O*-carbamoyl-α-D-mannopyranosyl trichloroacetimidate (30): **29** (2.57 g, 5.21 mmol) was reacted with CCl_3CN (0.61 mL, 6.10 mmol) and DBU (0.10 mL, 0.67 mmol) in CH_2Cl_2 (25 mL) at 0°C for 1 hr. Et_2O (30 mL) was added, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **30** (3.07 g, 92%) as a syrup. IR (neat) 3493, 3381, 3339, 3032, 2918, 2870, 1728, 1672, 1599, 1496, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.72 (1H, dd, *J*=1.9, 11.3Hz), 3.82 (1H, dd, *J*=4.0, 11.3Hz), 4.03 (1H, ddd, *J*=1.9, 4.0, 9.7Hz), 4.12 (1H, dd, *J*=2.4, 3.3Hz), 4.14 (1H, dd, *J*=9.0, 9.7Hz), 4.52 (2H, m), 4.60-4.71 (5H, m), 4.76 (1H, d, *J*=12.1Hz), 5.21 (1H, dd, *J*=3.2, 9.0Hz), 6.37 (1H, d, *J*=2.4Hz), 7.20-7.38 (20H, m), 8.59 (1H, s).

(1'*R*,2*R*,2'*R*,4*R*,5*S*)-5-Acetoxy-4-[1-benzyloxy-2-(2,4,6-tri-*O*-benzyl-3-*O*-carbamoyl-α-D-mannopyranosyl)oxy-3-butenyl]-2-phenyl-1,3-dioxane (31): BF_3•OEt_2 (0.61 mL, 5.0

mmol) was added to a mixture of **21** (988.0 mg, 2.48 mmol) and **30** (1.79 g, 2.81 mmol) in CH_2Cl_2 (20 mL) at -15°C, and the mixture was stirred at that temperature for 10 min. The reaction was quenched with sat. $NaHCO_3$ and the product was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **31** (1.78 g, 82%) as a syrup. $[\alpha]_D^{20}$ +33.9° (*c* 1.04, $CHCl_3$): IR (neat) 3493, 3373, 3032, 2914, 2868, 1736, 1599, 1496, 1454cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.10 (3H, s), 3.62 (1H, br, *J*=10.8Hz), 3.76 (1H, dd, *J*=3.7, 10.8Hz), 3.80 (1H, ddd, *J*=1.5, 3.7, 9.5Hz), 3.88 (1H, dd, *J*=2.0, 3.2 Hz), 3.91 (1H, dd, *J*=1.9, 8.3Hz), 4.01 (1H, dd, *J*=1.5, 13.1Hz), 4.06 (2H, m), 4.20 (1H, br, *J*=7.2Hz), 4.30 (1H, dd, *J*=1.5, 13.1Hz), 4.45-4.73 (11H, m), 5.04 (1H, d, *J*=2.0Hz), 5.16 (1H, dd, *J*=3.2, 9.6Hz), 5.18 (1H, br, *J*=10.4Hz), 5.25 (1H, br, *J*=17.4Hz), 5.59 (1H, s), 5.93 (1H, ddd, *J*=7.2, 10.4, 17.4Hz), 7.19-7.41 (25H, m): *Anal.* Calcd for $C_{51}H_{55}NO_{12}$: C, 70.09; H, 6.34; N, 1.60%. Found: C, 69.84; H, 6.54; N, 1.49%.

(1'*R*,2*R*,2'*R*,4*R*,5*S*)-4-[1-benzyloxy-2-(2,4,6-tri-*O*-benzyl-3-*O*-carbamoyl-α-D-mannopyranosyl)oxy-3-butenyl]-5-hydroxy-2-phenyl-1,3-dioxane (32): A mixture of **31** (148.4 mg, 0.170 mmol) and K_2CO_3 (44.0 mg) in MeOH (2 mL) was stirred at 60°C for 10 min. After being neutralized with AcOH, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **32** (131.4 mg, 93%) as a syrup. $[\alpha]_D^{20}$ +12.4° (*c* 1.04, $CHCl_3$): IR (neat) 3398, 2922, 2851, 1718, 1655, 1560, 1496, 1458cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.02 (1H, d, *J*=10.0Hz, OH), 3.58 (1H, br, *J*=10.0Hz), 3.64 (1H, dd, *J*=1.9, 10.9Hz), 3.77 (1H, dd, *J*=4.3, 10.9Hz), 3.85 (1H, dd, *J*=3.0, 7.4Hz), 3.88 (1H, dd, *J*=2.1, 3.2Hz), 3.89 (1H, m), 3.94 (1H, dd, *J*=1.0, 7.4Hz), 3.95 (1H, dd, *J*=1.2, 12.0Hz), 4.03 (1H, t, *J*=9.5Hz), 4.11 (1H, dd, *J*=1.9, 12.0Hz), 4.39 (1H, dd, *J*=3.0, 7.5Hz), 4.46-4.59 (6H, m), 4.62-4.73 (4H, m), 5.10 (1H, d, *J*=2.1Hz), 5.20 (1H, dd, *J*=3.2, 9.2 Hz), 5.22 (1H, br, *J*=10.4Hz), 5.29 (1H, br, *J*=17.2Hz), 5.55 (1H, s), 6.04 (1H, ddd, *J*=7.5, 10.4, 17.2 Hz), 7.20-7.53 (25H, m).

3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2,4,6-tri-*O*-benzyl-3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (33): **32** (1.61 g, 1.94 mmol) was reacted with O_3 in a manner similar to the preparation of **13** to give **33** (1.51 g, 94%) as an anomeric mixture (α/β=5/3). SI-MS (3-NBA, NaCl) *m/z* 856 ([M+Na]$^+$); *Anal.* Calcd for $C_{48}H_{51}NO_{12}$: C, 69.13; H, 6.16; N, 1.68%. Found: C, 68.83; H, 6.28; N, 1.55%.

1,3,4,6-Tetra-*O*-acetyl-2-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (34): **33** (158.4 mg, 0.190 mmol) in MeOH (3 mL) was stirred under H_2 in the presence of 20% $Pd(OH)_2$ (15.4 mg) to give unprotected mannogulose (69.1 mg, 94%) as a solid. Mannogulose (266.9 mg, 0.692 mmol) prepared in a similar manner was dissolved in pyridine (5 mL), and was added Ac_2O (0.80 mL, 8.5 mmol). The mixture was stirred at r.t. for 10 hr, and was poured into sat. $NaHCO_3$. The product was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane) to give **34** (446.9 mg, 95%) as a syrup. $[\alpha]_D^{20}$ +35.5° (*c* 0.95, $CHCl_3$): IR (neat) 3481, 3381, 2959, 1749, 1608cm^{-1}: ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.05 (3H, s), 2.06 (3H, s), 2.12 (3H, s), 2.13 (3H, s), 2.14 (3H, s), 2.15 (3H, s), 2.20 (3H, s), 4.00 (1H, dd, *J*=3.3, 8.4Hz), 4.06-4.29 (5H, m), 4.36 (1H, m), 4.64 (2H, br), 5.00 (1H, d, *J*=1.6Hz), 5.02 (1H, dd, *J*=1.4, 3.9Hz), 5.08 (1H, dd, *J*=3.4, 10.0Hz), 5.12 (1H, dd, *J*=1.8, 3.4Hz), 5.26 (1H, t, *J*=10.0Hz), 5.44 (1H, t, *J*=3.4Hz), 5.89 (1H, d, *J*=8.4Hz).

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References and Notes

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16. Numberings are expressed according to those of L-gulose or D-mannose in this paper.
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