Direct Syntheses of β-Mannopyranosyl Disaccharides from 4,6-*O*-Benzylidene Derivatives of Ethylthio α-D-Mannopyranosides Donors

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β-D-Mannopyranosyl disaccharides have been obtained from the coupling of 4,6-*O*-benzylidene derivatives of ethylthio α-D-mannopyranoside employing NIS-TfOH promoter. NIS-TfOH promoted couplings of the corresponding ethylthio β-D-glucopyranoside and produced α-D-glucopyranosyl disaccharides. IDCP (iodonium dicollidine perchlorate) was inactive toward the 4,6-*O*-benzylidenated ethylthio glucopyranosyl donor. However, IDCP coupled the 4,6-*O*-benzylidenated ethylthio-β-D-galactopyranoside to give α-D-galactopyranosyl disaccharides.

Introduction

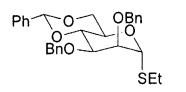
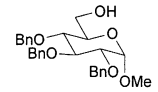
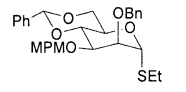
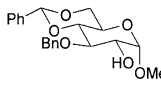
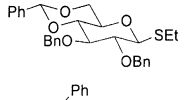
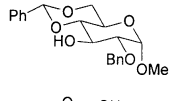
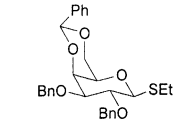
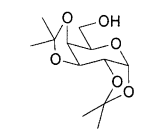
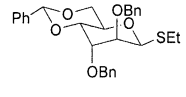
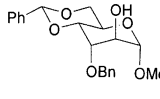
Glycosidation *via* traditional chemical methods by means of participation of a 2-*O*-acyl group of the glycosyl donor gives 1,2-trans glycosidic linkages resulting in β-*gluco*, β-*galacto* and α-*manno*pyranosides. On the other hand, the stereoselective introduction of 1,2-cis glycosidic bonds has been difficult to achieve in carbohydrate syntheses.[1] Among 1,2-cis glycosides, the formation of β-D-*manno*pyranosidic (β-D-Man*p*) linkages has been one of the most challenging tasks due to their axial 2-OH group, which stabilizes its α-anomer even further than the anomeric effect showed in corresponding α-*gluco* or α-*galacto*pyranosides. So far β-D-Man*p* linkages have been made in indirect syntheses such as intramolecular aglycon delivery method[2-7] or epimerization[8] of the 2-OH of the corresponding β-D-Glc*p* derivatives *via* oxidation-reduction sequence.[9] Heterogeneous Ag-Zeolite catalyst[10-12] or insoluble promoter[13] silver silicate[11] have been reported to produce β-D-Man*p* linkages. Crich and Sun[14-17] reported a protocol for the direct synthesis of β-mannopyranosides from a highly reactive glycosyl donor, α-mannopyranosyl triflate, which was obtained from treating mannopyranosyl sulfoxide donor with triflic anhydride (Tf_2O), in the presence of 2,6-di-*tert*-butyl-4-methylpyridine.

β-D-Man*p* linkages have been identified in lipopolysaccharides of *Escherichia*[18,19] and *Salmonella*,[10,20,21] in capsular polysaccharides of *Klebsialla*,[22] and in the core of *N*-glycoproteins.[23-27] The biological activities of carbohydrates are known to be related to stability, immunogenicity and protein folding of those biopolymers. In the studies and applications of those biopolymers, it is desirable to synthesize the carbohydrates of designed structures and to develop an efficient and stereo-controlled coupling method[28] for β-D-man*p* linkage and other 1,2-cis glycosidic linkages.

Thio glycosides[29] with benzyl protecting groups have served as armed glycosyl donors in the presence of IDCP (iodonium dicollidine perchlorate),[30,31] giving α-D-Glc*p* disaccharides (1,2-cis stereochemical relationship). On the other hand, thioglucopyranosides of benzoyl protecting groups are disarmed donors that can not be activated by IDCP, but they can be activated by NIS-TfOH (*N*-iodosuccinimide-trifluoromethanesulfonic acid)[32-34] giving β-D-Glc*p* disaccharides (1,2-trans stereochemical relationship). The 2-OH protecting group of a donor directly governs the donor activity and the stereochemical outcome of its coupling reaction. Steric and electronic factors of other OH groups in a donor may also affect its coupling reaction. From our previous study,[35] we know IDCP is inactive in coupling ethylthio 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-mannopyranoside (**1**) and ethylthio 4,6-*O*-benzylidene-2-*O*-benzyl-3-*O*-MPM-α-D-mannopyranoside (**2**). However, compounds **1** and **2** were activated by MeOTf or DMTST to produce β-D-Man*p* disaccharides in 55% yields.[35] It is noteworthy that β-D-Man*p* disaccharides,[36-41] hardly obtainable by direct chemical syntheses,[42-46] were formed preferentially from 4,6-*O*-benzylidenated derivatives of thio mannoside, **1** and **2**.

In the present study, the use of NIS-TfOH[32-34] to synthesize β-D-Man*p* disaccharides will be described. And the effects of a 4,6-*O*-benzylidene group in thioglycoside donors

Figure 1. List of Compounds

NO.	Donor	NO.	Acceptor
1		6	
2		7	
3		8	
4		9	
5		10	

of *gluco* and *galacto* will also be examined on their iodonium-mediated glycosylation, employing IDCP and NIS-TfOH promoters.

Experimental Section

General. Concentration was performed under reduced pressure at below 40 °C (bath). CH_2Cl_2 and ether were dried over P_2O_5 and Na-benzophenone, respectively. Freshly distilled solvents were used for the reactions. NMR spectra were recorded in chloroform-*d* solution referenced to internal TMS (a JEOL JNM-LA 400 spectrometer). Assignments were based on DEPT, 2D Cosy and 2D Heterocosy experiments. Flash column chromatography was performed on silica gel Merck 60 (Art 7734 70-230 mesh or Art 9385 230-400 mesh) with toluene-EtOAc (15 : 1, v/v) as a eluent. TLC was conducted on plates coated with a 0.2 mm layer of silica gel $60F_{254}$ (Merck) with toluene-EtOAc (5 : 1, v/v) as a eluent; the components were located by charring the plate with 5% sulfuric acid.

Glycosylation reactions were performed in the following procedures, according to Table 1 unless otherwise stated.

Iodonium dicollidine perchlorate (IDCP).[47] To a solution of a donor (0.35 mmol) and an acceptor (0.27 mmol) in dichloromethane-ether (2 : 5, v/v, 10 ml) was added freshly powdered MS 5 Å, and the mixture was stirred for 30 min at room temperature. To the mixture the promoter (0.81 mmol) was added with stirring. Stirring was continued for the reaction time at given temperature (Table 1). The precipitate was filtered off through a celite pad, and washed thoroughly with dichloromethane. The filtrate and washings were combined, and the solution was successively washed with 1 M $Na_2S_2O_3$ solution and water, dried (Na_2SO_4), concentrated, and purified on silica gel column.

***N*-Iodosuccinimide-trifluoromethanesulfonic acid (NIS-TfOH).** To a solution of a donor (0.46 mmol) and an acceptor (0.36 mmol) in dichloromethane (10 mL) was added freshly powdered MS 4 Å, and the mixture was stirred for 30 min at room temperature and then cooled to 0 °C. NIS (0.91 mmol) and tritluoromethanesulfonic acid (TfOH; 0.12 mmol) were added to the cooled mixture. The mixture was stirred for the reaction time (Table 1) at 0 °C, and the reaction was monitored by TLC. The mixture was filtered through a celite pad and washed thoroughly with dichloromethane. The filtrate and washings were combined, and the solution was successively washed with 1 M $Na_2S_2O_3$, $NaHCO_3$ solution and water, dried (Na_2SO_4), concentrated, and purified on silica gel column.

Methyl *O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (D1α) and methyl *O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (D1β). Glycosidation of **1** (109 mg) with **6** (93.4 mg) using NIS-TfOH yielded a mixture, which was flash chromatographed to give **D1α** (17.0 mg, 10%) and **D1β** (121 mg, 67%); R_f 0.73 for **1**, 0.13 for **6**, 0.50 for **D1α**, and 0.40 for **D1β**; ^{13}C NMR ($CDCl_3$, 100 MHz) for **D1α** δ 138.6-126.1 (aromatic C), 101.5 ($C_6H_5\underline{C}H$), 99.62 (C-1'), 97.74 (C-1), 82.02, 79.97, 79.11, 77.56, 76.38, 75.76, 75.70, 75.06, 73.41, 73.21, 73.01, 69.74, 68.77, 66.05, 64.32, 55.04 (OCH_3), $[\alpha]_D^{24}$ −49.7 (*c* 0.60, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) for **D1β** δ 138.7-125.9 (aromatic C), 101.8 (C-1'), 101.3 ($C_6H_5\underline{C}H$), 97.72 (C-1), 82.08, 79.67, 78.54, 77.71, 77.22, 75.59, 75.48, 74.57, 74.40, 73.20, 72.40, 69.51, 68.42, 68.09, 67.42, 54.98 (OCH_3), $[\alpha]_D^{24}$ -2.07 (*c* 1.99, $CHCl_3$).

Methyl *O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (D2α) and methyl *O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (D2β). Glycosidation of **1** (90.3 mg) with **7** (62.1 mg) using NIS-TfOH yielded a mixture. Flash chromatography gave a mixture (86.0 mg, 64%) of **D2α** and **D2β** in a ratio of 1:2.1; R_f 0.73 for **1**, 0.18 for **7**, 0.52 for a mixture of **D2α** and **D2β**; ^{13}C NMR ($CDCl_3$, 100 MHz) for **D2α** δ 129.0-125.2 (aromatic C), 101.4 and 101.3 ($C_6H_5\underline{C}H$), 96.91 (C-1'), 96.32 (C-1), 81.97, 79.59, 79.17, 78.39, 76.58, 75.52, 74.27, 73.95, 73.26, 68.85, 68.51, 64.14, 62.22, 55.19 (OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for **D2β** δ 128.8-126.0 (aromatic C), 103.0 (C-1'), 101.4 and 101.3 ($C_6H_5\underline{C}H$), 100.2 (C-1), 82.59, 78.89, 78.34, 78.04, 76.01, 75.24, 74.88, 73.50, 72.42, 69.10, 68.38, 67.46, 62.30, 55.38 (OCH_3).

Methyl *O*-(2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-*p*-methoxybenzyl-α-D-mannopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (D3α) and methyl *O*-(2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-*p*-methoxybenzyl-β-D-mannopyranosyl)-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (D3β). Glycosidation of **2** (196 mg) with **8** (127 mg) using NIS-TfOH yielded a mixture. Flash chromatography gave **D3α** (59.6 mg, 21%) and **D3β** (196 mg, 69%); R_f 0.68 for **2**, 0.32 for **8**, 0.58 for **D3α**, and 0.53 for **D3β**; ^{13}C NMR ($CDCl_3$, 100 MHz) for **D3α** δ 159.0-113.7 (aromatic C), 101.7 and 101.4 ($C_6H_5\underline{C}H$), 99.01 (C-1'), 98.74 (C-1), 82.62, 79.03, 77.47, 76.20, 75.31, 73.95, 73.57, 72.52, 72.33, 69.05, 68.77, 64.26, 61.73, 55.34 and 55.18 ($O\underline{C}H_3$ and $\underline{C}H_3OC_6H_4$); ^{13}C NMR ($CDCl_3$, 100 MHz) for **D3β** δ 159.1-113.7 (aromatic C), 103.0 (C-1'), 101.3 and 101.1 ($C_6H_5\underline{C}H$), 98.49 (C-1), 79.97, 79.85, 78.82, 78.58, 77.75 and 74.45 (C-2, 2', 3, 3', 4 and 4'), 73.37 ($C_6H_5\underline{C}H_2$), 72.14 ($CH_3OC_6H_4\underline{C}H_2$), 68.85, 68.69, 67.35 and 62.49 (C-5, 5', 6 and 6'), 55.27 and 55.18 (OCH_3 and $\underline{C}H_3OC_6H_4$).

Methyl *O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (D4α). Glycosidation of **3** (201 mg) with **6** (146 mg) using NIS-TfOH yielded a product. Flash chromatography gave **D4α** (274 mg, 98%); R_f 0.67 for **3**, 0.15 for **6** and 0.50 for **D4α**; ^{13}C NMR ($CDCl_3$, 100 MHz) for **D4α** δ 138.7-125.9 (aromatic C), 101.12 ($C_6H_5\underline{C}H$), 98.03 (C-1'), 97.84 (C-1), 82.00 (C-4'), 81.95 (C-3), 79.87 (C-2), 79.14 (C-2'), 77.74 (C-3'), 77.52 (C-4), 75.60, 74.91, 74.90, 73.22 and 72.69 ($C_6H_5\underline{C}H_2$), 70.20 (C-5), 68.92 (C-6'), 66.14 (C-6), 62.40 (C-5'), 55.08 ($O\underline{C}H_3$), $[\alpha]_D^{24}$ −38.7 (*c* 2.64, $CHCl_3$).

2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyra-

nose (D5α). Glycosidation of **3** (168 mg) with **9** (72 mg) using NIS-TfOH yielded a product. Flash chromatography gave **D5α** (161 mg, 84%): R_f 0.78 for **3**, 0.14 for **9**, and 0.63 for **D5α**; ^{13}C NMR ($CDCl_3$, 100 MHz) for **D5α** δ 138.8-125.9 (aromatic C), 109.1 ($\underline{C}_a(CH_3)_2$), 108.5 ($\underline{C}_b(CH_3)_2$), 101.1 ($C_6H_5\underline{C}H$), 98.20 (C-1'), 96.19 (C-1), 81.97, 79.16, 78.40, 75.08, 72.73, 70.71, 70.51, 70.50, 68.88, 66.77, 65.82, 62.34, 26.03, 25.94, 24.80 and 24.49 ($C(\underline{C}H_3)_2$), $[\alpha]_D^{24}$ -18.7 (*c* 2.12, $CHCl_3$).

Methyl *O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranosyl)-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-altropyranoside (D6α). Glycosidation of **4** (130 mg) with **10** (70 mg) using IDCP yielded a mixture. Flash chromatography gave **D6α** (140 mg, 65%): R_f 0.52 for **4**, 0.10 for **10**, and 0.23 for **D6α**; ^{13}C NMR ($CDCl_3$, 100 MHz) for **D6α** δ 138.6-125.2 (aromatic C), 102.0 and 100.9 ($C_6H_5\underline{C}H$), 100.6 (C-1), 98.73 (C-1'), 76.89, 76.19, 75.62, 75.16, 74.21, 73.55, 72.73, 71.99, 71.61, 69.22, 63.33, 58.49 (C-5), 55.53 (OCH_3).

Results and Discussion

NIS-TfOH was examined for its thiophilic activity toward trans bicyclic 4,6-*O*-benzylidenated derivatives of *manno* **1** and **2**, and that of *gluco* **3**. NIS-TfOH promoter coupled ethylthio 4,6-*O*-benzylidenated α-D-mannopyranosyl donor (**1** and **2**) with glucopyranosyl acceptors having a free OH at C-6 (**6**), C-2 (**7**) and C-3 (**8**), respectively.

From these reactions mannosyl disaccharides, Man6Glc (entry 1), Man2Glc (entry 2) and Man3Glc (entry 3) (Table 1) were obtained in 77, 64 and 90% yields, respectively.

Table 1. Coupling of Thioglycosyl donors with acceptors in CH_2Cl_2

Entry	Donor	Acceptor	Promoter	Sol. (v/v)	Temp.	Time	Disaccharide: % yield (α/β)
1	**1**	**6**	NIS-TfOH	C	0 °C	1min	**D1α**: Manα6Glc **D1β**: Manβ6Glc 77 (1/7.1)
2	**1**	**7**	NIS-TfOH	C	0 °C	1min	**D2α**: Manα2Glc **D2β**: Manβ2Glc 64 (1/2.1)
3	**2**	**8**	NIS-TfOH	C	0 °C	1min	**D3α**: Manα3Glc **D3β**: Manβ3Glc 90 (1/3.3)
4	**3**	**6**	NIS-TfOH	C	0 °C	1min	**D4α**: Glcα6Glc 98 (1/0)
5	**3**	**9**	NIS-TfOH	C	0 °C	1min	**D5α**: Glcα6Gal 84 (1/0)
6	**3**	**6**	IDCP	C-E (2/5)	r.t.	42 hr	No reaction
7	**4**	**10**	IDCP	C-E (2/5)	r.t.	2 hr	**D6α**: Galα2Alt 65 (1/0)
8	**5**	**8**	IDCP	C-E (2/5)	r.t.	24 hr	No reaction

(1) No reaction means starting compounds were recovered.
(2) Solvents C for CH_2Cl_2, E for Et_2O.

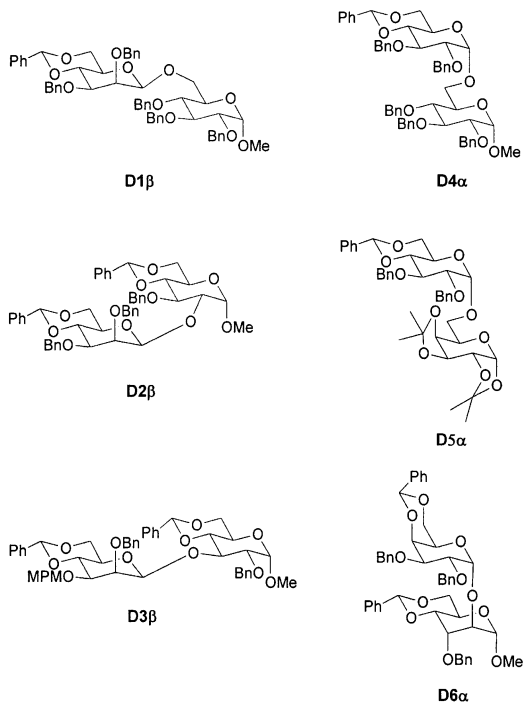


Figure 2. List of Disaccharides.

Reactions took place in one minute at 0 °C as showed in Table 1. Compared with the previous results[35] about IDCP, MeOTf and DMTST, NIS-TfOH is definitely an excellent promoter toward the 4,6-*O*-benzylidenated ethylthio α-D-mannopyranoside donors **1** and **2**. The preponderant formation of β-D-Man*p* disaccharides *via* inversion at the C-1 was also observed as it was with MeOTf and DMTST promoters.[35] However, such preponderance for β-mannosyl linkages appears to decrease with the steric hindrance of the attacking acceptor OH by obtaining Man6Glc, Man2Glc and Man3Glc in α/β ratios of 1/7.1, 1/2.1 and 1/3.3, respectively.

Activation by NIS-TfOH of trans bicyclic ethylthio glycoside donors was also confirmed with *gluco* derivative **3**; IDCP was inactive toward ethylthio 4,6-*O*-benzylidenated β-D-glucosyl donor **3**, which in the presence of NIS-TfOH was coupled with the 6-OH of glucosyl acceptor **6** and also with the 6-OH of galactosyl acceptor **9**. Only α-Glc*p* disaccharides, Glcα6Glc **D4α** and Glcα6Gal **D5α**, were produced in 98 and 84% yields, respectively. α-D-Gluc*p* disaccharides must have been formed via S_N2 or S_N2-like mechanism through inversion at the C-1 of the trans bicyclic ethylthio β-D-glucosides donors. The yields of α-D-Glc*p* disaccharides appear to decrease with the steric crowdedness of the acceptor OH: **9** (6-OH of Gal), bulkier than **6** (6-OH of Glc), showed a lower yield. IDCP was found to be inactive[35] toward another rigid trans bicyclic compound, ethylthio

Table 2. ^{13}C NMR data for disaccharides (δ in ppm) in $CDCl_3$

	D1α	**D1β**	**D2α**	**D2β**	**D3α**	**D3β**	**D4α**	**D5α**	**D6α**
C-1	97.7	97.7	96.3	100.2	98.7	98.5	97.8	96.2	100.6
C-1'	99.6	101.8	96.9	103.0	99.0	103.0	98.0	98.2	98.7

C-1' denotes for the glycosylated anomeric carbon.

4,6-*O*-benzylidene-2,3-di-*O*-benzyl-β-D-altropyranoside (**5**). However, IDCP was active in the coupling of cis-bicyclic ethylthio 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-β-D-galactopyranoside (**4**) with methyl 4,6-*O*-benzylidene-3-O-benzyl-α-D-altropyranoside (**10**) to an α-Gal*p* disaccharide **D6α**.

Anomeric assignments of Man*p*, Glc*p* and Gal*p* disaccharides are based on the ^{1}H- and ^{13}C NMR data (Table 2) together with their specific rotations. As was observed previously, C-1 signals of α-Man*p* disaccharides appear at higher field than those of their β-Man*p* anomers by 2-6 ppm, and specific rotation values of the former are higher than those of the latter.[16,17, 48,49]

IDCP promoted glycosidation from perbenzylated ethylthio β-D-*gluco* or *galacto*pyranosides gives 1,2-cis glycosides, *i.e.*, α-Glc*p* and α-Gal*p*[35] *via* S_N2 or S_N2-like mechanism. However, when perbenzylated ethylthio α-D-*manno*pyranosides are treated with IDCP, α-Man*p* disaccharides with retention at the anomeric carbon are obtained exclusively. That is, α-Man*p* disaccharides, thermodynamically favored by the anomeric effect and the mannosyl 1,2-trans-OH relationship, were obtained from the glycosidation of perbenzylated ethylthio α-D-*manno*pyranoside *via* S_N1 or S_N1-like mechanism.

On the other hand, NIS-TfOH promoted glycosidation of the 4,6-*O*-benzylidenated derivatives of ethylthio α-D-*manno*-pyranoside produced β-Man*p* disaccharides *via* S_N2-like pathways (Figure 3). Considering the inherent difficulty with the stereoselective formation of β-D-Man*p* linkages, these findings are extremely important in carbohydrate syntheses. Sun and Crich[14-17] succeeded in obtaining β-D-Man*p* from phenylthio 4,6-*O*-benzylidenated mannopyranoside derivative with PhSOTf at -78 °C, but use of NIS-TfOH promoter at 0 °C is much easier to handle. The stereoselectivity of glycosidation improved when the solvent was changed from CH_2Cl_2-Et_2O (2/5) to CH_2Cl_2 and governed by the substitients of the sugar acceptor.

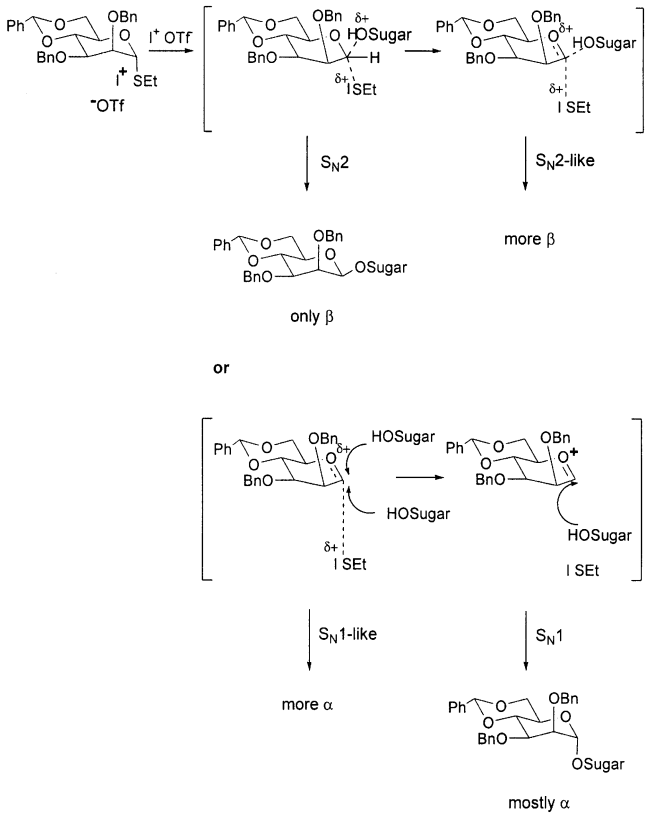


Figure 3. Probable Stereochemistry of Mannopyranosyl Disaccharides depending on Reaction pathways.

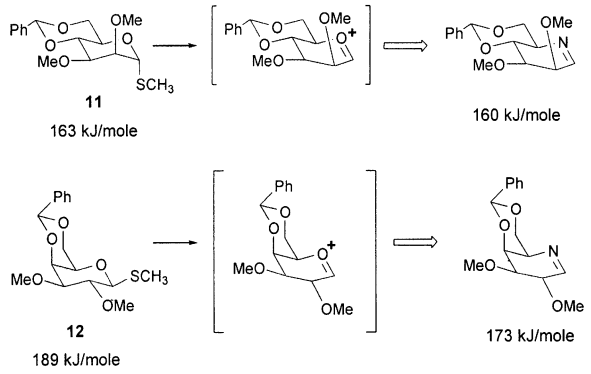


Figure 4. Energy Differences obtained from the Calculation using MM3 program.

The present results show the trans bicyclic system of mannosyl donors **1** and **2** to be an important factor in their low donor reactivity and in their exclusive transformation to β-D-Man*p* disaccharides. Conformational flexibility of the thioglycosides donor may be a measure of IDCP promoted glycosidation; the *galacto* **4** being conformationally flexible showed donor activity by IDCP, while *altro* **5**, *gluco* **3** or *manno* **1** and **2** being rigid did not.

However, it is also possible that the relative instability of the cis bicyclic *galacto* (**4**) to the trans bicyclic *manno* (**1** and **2**) is the driving force for the IDCP promoted glycosidation. Using the MM3 program we calculated the energy difference (26 kJ/mole) between the trans bicyclic *manno* **11** and the cis bicyclic *galacto* **12**. Since the energies of oxonium ion intermediates were impossible to obtain, the corresponding cyclo-imine systems were used (Figure 4). The energy difference (13 kJ/mole) between the trans and cis bicyclic imines is considerably lower than that (26 kJ/mole) between the corresponding thioglycosides. It may be concluded that IDCP is not a strong enough activator to cleave the thioglycosidic linkages of trans bicyclic ethylthio 4,6-*O*-benzylidenated *manno* (**1**, **2**), *gluco* (**3**) and *altro* (**5**) derivatives.

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