Highly Optimized β-Mannosylation via *p*-Methoxybenzyl Assisted Intramolecular Aglycon Delivery

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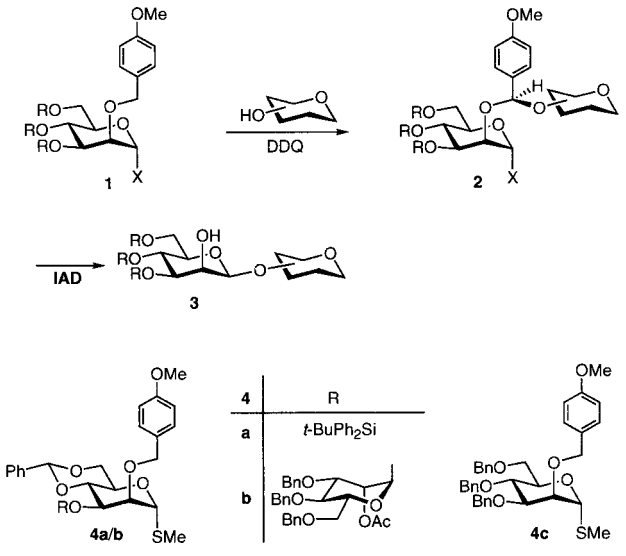
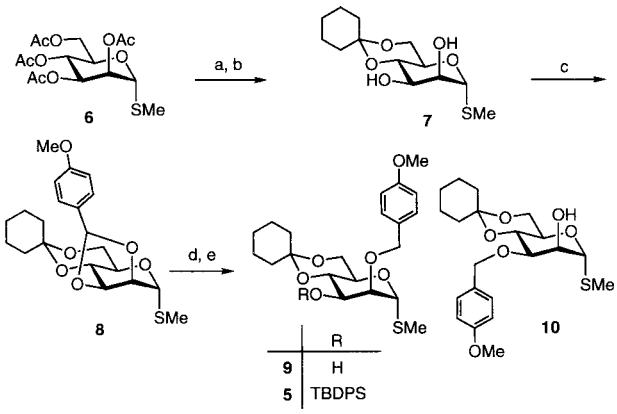
Abstract: Highly efficient and stereoselective *β*-mannosylation was achieved by using mannosyl thioglycosides **5** and **19**. Intramolecular aglycon delivery (IAD) from mixed acetal **12**, **15** and **20**, obtainable by oxidative coupling of aglycon onto mannosyl thio-glycosides which carry *p*-methoxybenzyl (PMB) group at C-2 position, was performed by the action of $MeOSO_2CF_3$ to afford *β*-mannosides **13**/**16**/**21**. It is to be noted that efficiency of IAD was substantially improved by changing the protecting group at the 4- and 6- positions from previously utilized benzylidene to cyclohexylidene (**5**) or TIPDS (**19**) group. As a result, it is now possible to perform the *β*-manno glycosylation in a highly optimized manner to afford di- and trisaccharides with a backbone structure corresponding to asparagine-linked oligosaccharides in 75-85% yield as single stereoisomers.

In 1994, we reported a novel strategy[1] for the stereoselective synthesis of β-manno glycoside[2], as a new entry into the so called intramolecular aglycon delivery (IAD)[3] approach. In our version of IAD, *p*-methoxybenzyl (PMB) group at 2-position of mannosyl donor **1** functions as a scaffold for the DDQ mediated[4] formation of the tethered intermediate **2**. Subsequent activation of the anomeric position triggers IAD to afford β-manno glycoside **3** (**Scheme 1**). This strategy was subsequently applied to the completely stereocontrolled synthesis of the core structure of asparagine (Asn) linked glycoprotein oligosaccharides[5]. Selectively protected thioglycosides **4a**/**b** were used as mannosyl donors to afford di-, tri- and tetrasaccharide products in 49-60% yield. We report here the highly optimized version of PMB assisted IAD protocol which gives >80% yield of β-mannosides corresponding to the common structural units of Asn-linked oligo-saccharides [i.e. βMan1-4βGlcNAc(±1-4GlcNAc)].



Scheme 1

At the earlier stage of our investigation by using 4,6-benzylidene protected (**4a**/**b**) as well as tribenzylated (**4c**) donors, it was quickly recognized that having a cyclic 4,6-*O*-protection is important in IAD using thioglycosides[6]. This observation lead us to the working hypothesis that the rigidity of hexopyranoside chair conformation may be responsible for successful IAD starting from **4a**/**b**. Therefore, 4,6-*O*-cyclohexylidene protected **5** was designed, in which $^4C_1$ form should be frozen more rigidly compared to **4a**. Preparation of **5** was performed as depicted in **Scheme 2**. Thus, starting from methyl-thiomannoside **6**[7], cyclohexylidene group was installed to give **7**. Subsequent formation of 2,3-*O*-*p*-methoxybenzylidene acetal was effected under Yonemitsu's conditions[8] to afford **8** (77% yield), that was subjected to the reductive ring opening process effected by DIBAL which gave 2-*O*-PMB protected **9** in 60% yield as well as a minor amount of **10** in ca. 5:1 ratio. Further protection of the 3-position afforded **5**[9,10].

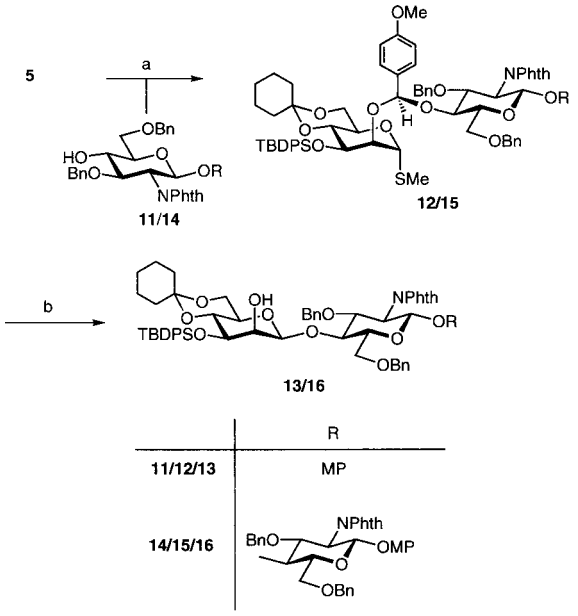


Reagents and conditions: (a) NaOMe, MeOH; (b) 1,1-dimethoxycyclohexane CSA, DMF, 50-55 °C, 3 h, 76% (2 steps); (c) *p*-$MeOC_6H_4CH_2OMe$, DDQ, MS 4A CH_2Cl_2, r.t., 18 h, 77%; (d) DIBAL, toluene, -40 °C, 0.5 h, 60%; (e) *t*-$BuPh_2SiCl$ imidazole, DMF, 50 °C, 18 h, 84%

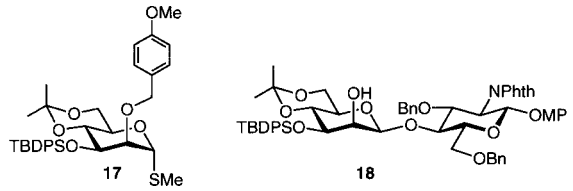
Scheme 2

β-Mannosylation by using **5** was examined under our standard conditions and proved to be highly efficient. (**Scheme 3**) Thus, treatment of glucosamine derived acceptor **11**[11] with **5** (1.3 equiv.) and DDQ (1.5 equiv.) in CH_2Cl_2 (25 ml/mmol of **11**) in the presence of molecular sieves 4A (room temp. 2 h) afforded mixed acetal **12** in an essentially quantitative yield (based on ^{1}H-NMR analysis). Subsequent IAD was effected by methyl trifluoromethanesulfonate[12] (MeOTf) and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) in 1,2-dichloroethane (ca. 10 mM concentration of **12**; 45°C, 24 h) to afford an 83% yield of disaccharide **13**[10] which corresponds to βMan1-4GlcNAc. In a similar manner, the reaction with disaccharide **14**[11] gave **16**[10] via **15**[10] in 85% yield.

4,6-*O*-Isopropylidene protected donor **17**, which was prepared from **5** (1. CSA/MeOH; 2. $Me_2C(OMe)_2$, CSA/MeCN), gave a less satisfactory result (61% yield of **18**[10]). Comparison of yields obtained by



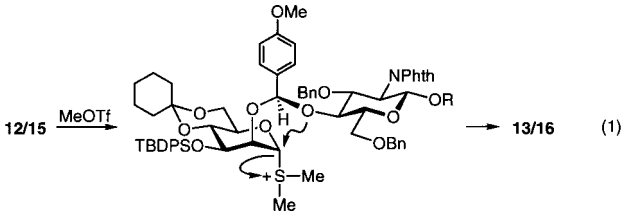
Reagents and conditions: (a) **11** or **14**, DDQ, MS 4A, CH_2Cl_2, r.t., 2 h; (b) MeOTf, DBMP, MS 4A, $Cl(CH_2)_2Cl$, 45 °C, 24 h, 83% (**13**), 85% (**16**)



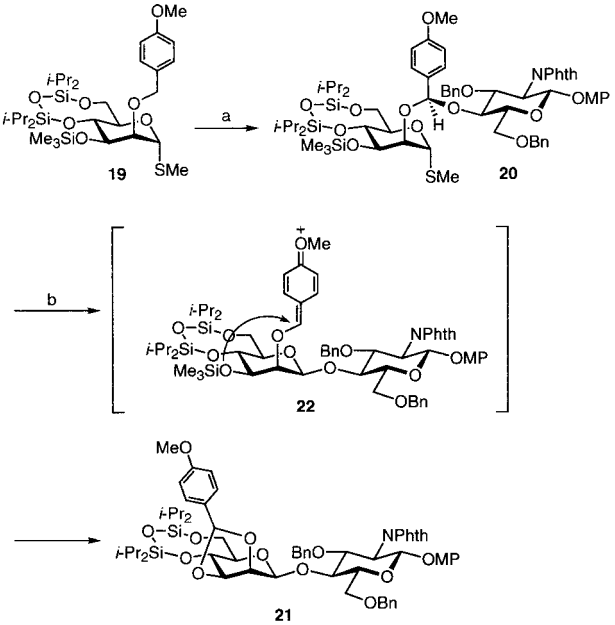
Scheme 3

glycosylation of **11** using **4a** (60%), **5** (83%) and **17** (61%) suggests that rigidity of the pyranose ring system is actually a significant factor controlling the efficiency of our system.

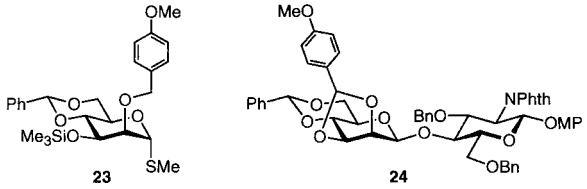
During the course of IAD, rigid chair conformation of mannose residue would encourage the S_N2 type reaction, thereby suppressing side reactions arising from oxocarbenium ion-like species[13] (**Eq. 1**).



On the other hand, 4,6-*O*-disiloxanylidene carrying **19** also gave us a highly satisfactory result (**Scheme 4**). Glycosyl donor **19** was assumed to represent the relaxed hexopyranose ring system compared to **4a**, **5** and **17**. Compound **19** was prepared from **6** in 5 steps (1. NaOMe, MeOH, 93%; 2. $TIPDSCl_2$, imidazole/DMF, 84%; 3. *p*-$MeOC_6H_4CH(OMe)_2$, PPTS/DMF, 85%; 4. DIBAL/toluene, 86%; 5. TMSCl, imidazole/DMF, 94%) and was subjected to the β-mannosylation conditions to react with **11**. Mixed acetal **20**[10] was isolated in 96% yield after purification by florisil and treated with MeOTf-DBMP to give **21**[10] in 78% yield, which can be compared quite favorably with the results obtained by **4a**/**17**. The higher efficiency observed here may be ascribed to the concomitant formation of cyclic acetal. In this case the 3-position of **19** is protected by trimethylsilyl and the *C*-3 oxygen traps intramolecularly the immediate product **22** to neutralize the positive charge effectively. Since similar transformation with 4,6-*O*-benzylidene counterpart **23** gave lower yield (55%) of the product **24**, having a larger ring system bridging the 4- and 6-positions seems to be beneficial for the ring closure step.



Reagents and conditions: (a) **11**, DDQ, MS 4A, CH_2Cl_2, r.t., 2 h, 96%; (b) MeOTf, DBMP, MS 4A, $Cl(CH_2)_2Cl$, 60 °C, 14 h, 78%.



Scheme 4

Due to their protection patterns, the potential utility of β-mannoside products (**13**, **16**, **21**) in synthetic studies of Asn-linked oligosaccharides is obvious. In summary, fine-tuning of *p*-methoxybenzyl assisted β-mannosylation was successfully made by using a 4,6-*O*-cyclohexylidene (**5**) and -TIPDS (**19**) carrying mannosyl donor.

Typical β-mannosylation procedure: Preparation of **21***:* To a stirred mixture of compounds **19** (504 mg, 0.78 mmol) and **11** (580 mg, 0.98 mmol) in CH_2Cl_2 (15 ml) containing molecular sieves 4A was added DDQ (219 mg, 0.96 mmol) under positive flush of argon at 0°C. The mixture was stirred at room temperature for 2 h and quenched with an aqueous solution (10 ml) of ascorbic acid (0.7%)-citric acid (1.3%)-NaOH (0.9%). The resulting lemon-yellow mixture was diluted with ether and filtered through Celite. The filtrate was washed with aq. $NaHCO_3$ and brine, successively, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by chromatography on florisil (2-5% EtOAc in toluene) to afford 929 mg (96%) of mixed acetal **20**, which was transferred, as a solution in CH_2Cl_2 (90 ml), into the reaction flask containing DBMP (796 mg, 3.88 mmol) and molecular sieves 4A (3.5 g). Under ice-water cooling, MeOTf (1M in 1,2-dichloroethane, 3.0 ml, 3.0 mmol) was added and the whole was stirred at room temperature for

0.5 h and at 60°C for 14 h. The reaction was quenched with Et_3N (3 ml), diluted with ether and filtered through Celite. The filtrate was washed successively with aq. $NaHCO_3$, water and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed over silica gel (5-10% EtOAc in toluene) to afford 659 mg (78%; 75% over 2 steps) of compound **21**.

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References and Notes

1. Y. Ito, T. Ogawa, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1765-1767, *Angew. Chem.* **1994**, *106*, 1843-1845.
2. For recent publications, see; T. Iimori, H. Ohtake, S. Ikegami, *Tetrahedron Lett*. **1997**, *38*, 3415-3418; G. Hodosi, P. Kovác, *J. Am. Chem. Soc*. **1997**, *119*, 2335-2336; D. Crich, S. Sun, *J. Org. Chem*. **1997**, *62*, 1198-1199, and references cited therein. For enzymatic approaches, see; G. M. Watt, L. Revers, M. C. Webberley, I. B. H. Willson, S. L. Flitsch, *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2354-2356; N. Taubken, B. Sauerbrei, J. Thiem, *J. Carbohydr. Chem*.**1993**, *12*, 651-667; S. Singh, M. Scigelova, D. H. G. Crout, *Chem. Commun*. **1996**, 993-994.
3. F. Barresi, O. Hindsgaul, *J. Am. Chem. Soc*. **1991**, *113*, 9377-9379; F. Barresi, O. Hindsgaul, *Synlett* **1992**, 759-760; G. Stork, G. Kim, *J. Am. Chem. Soc*. **1992**, *114*, 1087-1088; G. Stork, J. J. La Clair, *J. Am. Chem. Soc*. **1996**, *118*, 247-248.
4. PMB group has been extensively used as a valuable hydroxy protecting group which can be removed by DDQ in water containing media: Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett*. **1982**, *23*, 885-888; T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, New York, **1991**, p. 53.
5. (a) A. Dan, Y. Ito, T. Ogawa, *J. Org. Chem*. **1995**, *60*, 4680-4681. (b) A. Dan, Y. Ito, T. Ogawa, *Tetrahedron Lett*. **1995**, *36*, 7487-7490. (c) Y. Ito, T. Ogawa, *J. Am. Chem. Soc*. **1997**, *119*, 5562-5566.
6. Reaction of **4a** and **4c** with **11** afforded 60% (ref. 5a) and 29% yield (A. Dan, Y. Ito, T. Ogawa, unpublished) of corresponding β-manno glycoside, respectively.
7. T. Ogawa, K. Katano, M. Matsui, *Carbohydr. Res*. **1978**, *64*, C3-C9; F. Yamazaki, S. Sato, T. Nukada, Y. Ito, T. Ogawa, *Carbohydr. Res*. **1990**, *201*, 31-50.
8. Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett*. **1982**, *23*, 889-892.
9. Preparation of **5** can be conveniently performed in 35 % overall yield from **7**, without isolation of intermediates **8** and **9**.
10. Selected NMR data ($CDCl_3$) are given for key compounds. **5**: δ_H (270 MHz) 4.81 (1H, d, *J* = 1.3 Hz, H-1), 3.78 (3H, s, OMe), 3.22 (1H, br.s, H-2). 1.89 (3H, s, SMe), 1.12 (9H, s, *t*-Bu). **12**: δ_H (270 MHz) 5.59 (1H, d, *J* < 1 Hz, H-1^2), 5.59 (1H, d, *J* = 8.3 Hz, H-1^1), 5.42 (1H, s, acetal CH), 5.16 and 4.89 (each 1H, d, *J* = 13.2 Hz, benzylic CH_2), 3.78 (3H, s, OMe), 3.68 (3H, s, OMe), 1.90 (3H, s, SMe). **13**: δ_H (400 MHz) 5.55 (1H, d, *J* = 8.3 Hz, H-1^1), 4.36 (1H, s, H-1^2), 3.68 (3H, s, OMe), 1.11 (9H, s, *t*-Bu); δ_C (67.5 MHz) 100.2 ($^1J_{C\text{-}H}$ = 159 Hz, C-1^2), 99.8 (ketal C), 97.7 ($^1J_{C\text{-}H}$ = 165 Hz, C-1^1). **15**: δ_H (270 MHz) 5.66 (1H, s, H-1^3), 5.472 (1H, s, acetal CH), 5. 465 (1H, d, *J* = 8.2 Hz, H-1^1), 5.28 (1H, d, *J* = 8 Hz, H-1^2), 5.16 (1H, d, *J* = 13.2 Hz, benzylic CH), 3.72 (3H, s, OMe), 3.64 (3H, s, OMe), 1.69 (3H, s, SMe). **16**: δ_H (400 MHz) 5.44 (1H, d, *J* = 8.3 Hz, H-1^1), 5.23 (1H, d, *J* = 8.3 Hz, H-1^2), 4.43 (1H, s, H-1^3), 3.63 (3H, s, OMe), 1.11 (9H, s, *t* -Bu); δ_C (67.5 MHz) 100.1 ($^1J_{C\text{-}H}$ = 161 Hz, C-1^3), 99.8 (cyclohexylidene), 97.5, 96.7 ($^1J_{C\text{-}H}$ = 165, 167 Hz, C-$1^{1,2}$). **18**: δ_H (270 MHz) 5.56 (1H, d, *J* = 8.2 Hz, H-1^1), 4.42 (1H, s, H-1^2), 3.93 (1H, t, *J* = 9 Hz, H-4^2), 3.69 (3H, s, OMe), 2.80 (1H, m, H-5^2), 2.72 (1H, br, OH), 1.09 (9H, s, *t*-Bu); δ_C (67.5 MHz) 100.8 (C-1^2), 100.0 (isopropylidene), 98.2 (C-1^1). **19**: δ_H (270 MHz) 5.25 (1H, dd, *J* = 1.1 Hz, H-1), 4.60 (2H, s, CH_2Ar), 4.38 (1H, t, *J* = 9.2 Hz, H-4), 4.16 (1H, dd, *J* = 12.5, 1.7 Hz, H-6), 3.82 (1H, m, H-6'), 3.80 (3H, s, OMe), 3.73 (1H, m, H-5), 3.65 (1H, dd, *J* = 3.3, 1.1 Hz, H-2), 2.10 (3H, s, SMe). **20**: δ_H (270 MHz) 5.94 (1H, s, H-1^2), 5.81 (1H, s, acetal CH), 5.55 (1H, d, *J* = 8.2 Hz, H-1^1), 5.11 (1H, d, *J* = 12.5 Hz, benzylic CH), 3.81 (3H, s, OMe), 3.69 (3H, s, OMe), 2.21 (3H, s, SMe). **21**: δ_H (270 MHz) 5.94 (1H, acetal CH), 5.61 (1H, d, *J* = 8.6 Hz, H-1^1), 5.05 (1H, d, *J* = 12.9 Hz, benzylic CH), 4.90 (1H, br.s, H-1^2), 4.78 (1H, d, *J* = 12.0 Hz, benzylic CH), 4.70 (1H, d, *J* = 12.9 Hz, benzylic CH), 3.72 (3H, s, OMe), 3.70 (3H, s, OMe), 2.92 (1H, br.d, *J* = 10 Hz, H-3^2); δ_C (67.5 MHz) 104.4 (acetal carbon), 99.2 ($^1J_{C\text{-}H}$ =158 Hz, C-1^2), 97.6 ($^1J_{C\text{-}H}$ = 166 Hz, C-1^1).
11. **11**: T. Nakano, Y. Ito, T. Ogawa, *Carbohydr. Res*. **1993**, *243*, 43-69. **14**: H. Kuyama, Y. Nakahara, T. Nukada, Y. Ito, Y. Nakahara, T. Ogawa, *Carbohydr. Res*. **1993**, *243*, C1-C7.
12. H. Lönn, *J. Carbohydr. Chem*. **1987**, *6*, 301-306.
13. For a discussion on the role of 4,6-cyclic protection in β-mannosylation using glycosyl sulfoxide; see D. Crich, S. Sun, *J. Am. Chem. Soc*. **1997**, *119*, 11217-11223.