Glycosylation

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Stereoselective β-Mannosylation by Neighboring-Group Participation

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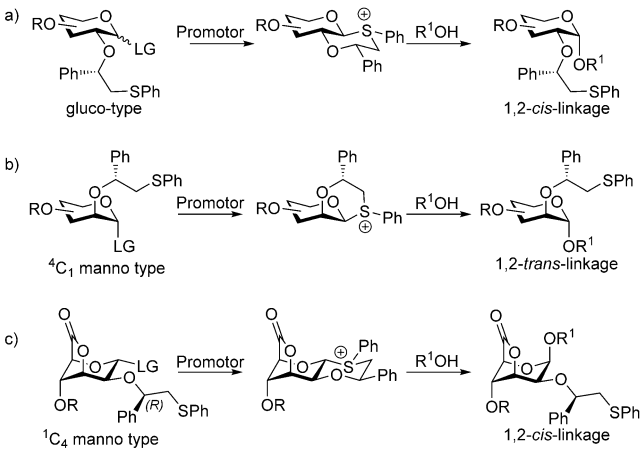
Abstract: *The stereoselective synthesis of glycosidic bonds is the main challenge of oligosaccharide synthesis. Neighboring-group participation (NGP) of C2 acyl substituents can be used to provide 1,2-trans-glycosides. Recently, the application of NGP has been extended to the preparation of 1,2-cis-glycosides with the advent of C2 chiral auxiliaries. However, this methodology has been strictly limited to the synthesis of 1,2-cis-gluco-type sugars. Reported herein is the design and synthesis of novel mannosyl donors which provide 1,2-cis-mannosides by NGP of thioether auxiliaries. A key element in the design is the use of $^1C_4$ locked mannuronic acid lactones to enable NGP of the C2 auxiliary. In addition to C2 participation a new mode of remote participation of the C4 benzyl group was identified and provides 1,2-cis-mannosides.*

The most challenging aspect of oligosaccharide synthesis is the stereoselective synthesis of glycosidic bonds.[1] For oligosaccharide synthesis to become a routine process, broadly applicable and highly reliable glycosylation methods are needed. In this respect, the most promising methodology is based on the neighboring-group participation (NGP) of C2 acyl substituents to provide 1,2-*trans*-glycosides.[1b] This methodology is broadly applicable to manno- and gluco-type sugars and has been applied to (automated) solid-phase oligosaccharide synthesis (SPOS).[2]

Recently, the application of NGP has been extended to the preparation of 1,2-*cis*-glycosides with the advent of C2 chiral auxiliaries (Scheme 1 a).[3] In this approach, a C2 (*S*)-(phenylthiomethyl)benzyl ether is used to trap the oxocarbenium ion from the β-face, thus resulting in the formation of 1,2-*cis*-glycosides. This methodology holds great promise to become a generally applicable principle for the synthesis of 1,2-*cis*-glycosides.[4] However, this methodology has been strictly limited to the synthesis of 1,2-*cis*-gluco-type sugars. The *trans*-decalin sulfonium ion intermediate is unlikely formed in mannose and the most likely intermediate would be a *cis*-decalin system, which would provide the 1,2-*trans*-mannoside instead (Scheme 1 b). Conversely, an alternative method to prepare β-mannosides has been developed by Crich and co-workers, but this method is mostly limited to the synthesis of β-mannosides.[5] We therefore explored the possibility of preparing β-mannosides using NGP since this method is applicable to other classes of carbohydrates as well.



Scheme 1. General overview of NGP in manno- and glucotype donors: a) Neighboring-group participation by a chiral auxiliary in gluco- and galacto-type donors resulting in the 1,2-*cis* product. b) C2 participation of the auxiliary in the $^4C_1$ conformation resulting in the *cis*-decalin system and hence 1,2-*trans*-mannosides. c) A ring flip into the $^1C_4$ conformation favors the *trans*-decalin system. Attack of the acceptor at the β position (axial) results in the β-mannoside. LG = leaving group.

Herein we report a new strategy to enable NGP for the synthesis of 1,2-*cis*-mannosides by use of the $^1C_4$ conformation. In this conformation, and using an *R*-configured auxiliary, the formation of a *trans*-decalin intermediate is possible (Scheme 1 c). We designed three mannose donors, **9a–c** (see Scheme 2) to study the effect of conformation on NGP and the stereoselectivity of the ensuing glycosylation.[6] To obtain the desired $^1C_4$ conformation, we used a 3,6-lactone bridge which can be introduced by oxidation of the 3,6-diol precursor using TEMPO/BAIB.[7] Critically, this mild oxidation method is chemoselective and compatible with thioethers.[8] Typically, the sulfonium ions are obtained after pre-activation of glycosyl imidates. However, early attempts to prepare glycosyl imidates of glycosyl lactones failed because the intermediate lactol underwent ring opening. Hence, we selected the carboxybenzyl leaving group as it is compatible with thioethers and can be introduced at an early stage.[9]

Synthesis of **9a–c** started from the known benzylidene protected thiomannosides **1a/b** (Scheme 2).[10] The benzylidenes in **1a/b** were reductively opened at C4 to give the corresponding 3,6-diols **2a/b**, which, after acetylation, afforded **3a/b** in good yields. The thiomannosides **3a/b** were used to glycosylate 2-(allylcarboxy)benzyl (ACB) alcohol using NIS/TfOH[11] to give **4a/b**. Next, the 2-methylnaphthyl ether of **4a** was cleaved by DDQ oxidation to give the alcohol **5**. The (*R*)-(phenylthiomethyl)benzyl ether was introduced with retention of stereochemistry by BF_3-Et_2O-promoted activation of (*R*)-1-phenyl-2-(phenylthio)ethyl acetate.[3a] To prepare the donor **9a**, **6** was deallylated with $[Pd(PPh_3)_4]$.

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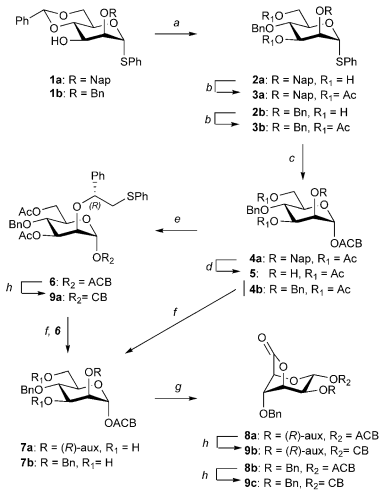


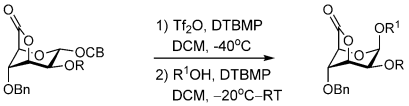
Scheme 2. Reagents and conditions: a) BH_3·THF, Bu_2BOTf, THF; **2a**, 97%; **2b**, 70%; b) Ac_2O, pyridine; **3a**, 95%; **3b** 95%; c) ACB, NIS, TfOH, DCM; **4a**, 82%; **4b**, 82%; d) DDQ, DCM/H_2O (7.5:1); **5**, 75%; e) (*R*)-PhCH(OAc)CH_2SPh, BF_3·Et_2O, DCM; **6**, 70%; f) AllylOH, KOtBu; **7a**, 85%; **7b**, 87% g) TEMPO, BAIB, H_2O/DCM (1:10); **8a**, 60%; **8b**, 80%; h) $[Pd(PPh_3)_4]$, AcOH/DCM (1:5); **9a**, 90%; **9b**, 90%, **9c**, 85%. ACB = allylcarboxybenzyl, BIAB = bis(acetoxy)iodobenzene, CB = carboxybenzyl, DCM = dichloromethane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Nap = 2-methylnaphthyl, NIS = *N*-iodosuccinimide, (*R*)-Aux = (*R*)-CH(Ph)CH_2SPh, TEMPO = 2,2,6,6,-tetramethylpiperidine-*N*-oxyl, Tf = trifluoromethanesulfonyl.

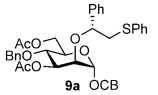
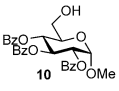
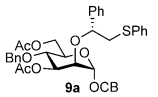
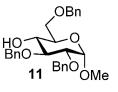
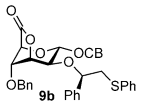
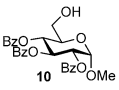
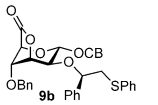
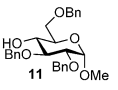
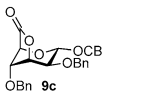
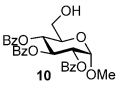
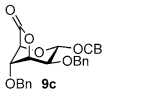
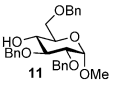
Next, **4b** and **6** were deacetylated using KO*t*Bu in allyl alcohol to obtain the diols **7a** and **7b**, respectively. Because the thioether moiety is readily oxidized using most traditional oxidation methods, the aforementioned chemoselective TEMPO/BAIB method was chosen.[7] Oxidation of **7a/b** (60–80%) proceeded with moderate yields to provide $^1C_4$ mannolactones **8a/b**. Finally, the compounds **8a/b** were deallylated to afford glycosyl donors **9b/c**.

Next, we glycosylated the donors **9a–c** with glycosyl acceptors **10** and **11** (Table 1, entries 1–6). The donors **9a–c** were preactivated at low temperature (−78 °C, −40 °C respectively) with 1.0 equivalents of Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a base. All donors were activated almost instantaneously and reactions with **9a** and **9b** were warmed to −20 °C before addition of the acceptor. As expected, **9a** produced mainly α-mannosides, presumably via a *cis*-decalin sulfonium ion intermediate (entries 1 and 2). In contrast, glycosylation with **9b** showed excellent β-selectivity in respectable yields (entries 3 and 4). The β-selectivity observed in these glycosylations supports the hypothesis that the reaction proceeds by an S_N2-like displacement of the proposed equatorial sulfonium ion.[12] However, **9c**, which because of the high reactivity was activated at lower temperature (−78 °C), produced exclusively β-mannosides with both the primary and secondary acceptor (entries 5 and 6).These results indicate that reactive intermediates other than the α-sulfonium ion are also important for the observed β-selectivity.

To explain the results of the glycosylations shown in Table 1, VT-NMR studies were performed on the donors **9a–c** to identify reaction intermediates. The $^4C_1$ donor **9a** was

Table 1: Glycosylation results for the donors **9a–c**.



Entry	Donor	Acceptor	Yield [%][a]	α/β[b]	$^1J_{C1\text{-}H1}$[c] [Hz]
1			82[d]	10:1	170
2			71[d]	>20:1	175
3			61[d] 52[e]	>1:20	172
4			58[d]	>1:20	176
5			87[d,f] 70[e]	>1:20	172
6			37[d]	>1:20	176

[a] Yield of isolated product. [b] Ratios determined by integration of key NMR signals of in the spectra of the crude reaction mixture. [c] The stereochemistry was determined by the $^1J_{C1,H1}$ coupling constant: axial H1 (≈160 Hz) or equatorial H1 (≈170 Hz)[13] [d] Used 2.0 equiv of glycosyl donor. [e] Used 2.0 equiv of acceptor. [f] Inseparable mixture with **14c.** Bz = benzoyl, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

mixed with 2.0 equivalents of DTBMP in CD_2Cl_2 at −20 °C and activated with 1.0 equivalents of Tf_2O in an NMR tube. At this temperature ^{1}H, ^{1}H-TOCSY, ^{1}H-^{13}C-HSQC, and ^{1}H-^{13}C-HMBC NMR spectra were recorded to confirm the identity of the intermediates present. HMBC analysis showed a C1–$H8_{ax}$ correlation, which confirmed the presence of the β-sulfonium ion as expected (see the Supporting Information).

As depicted in Figures 1a–d, the $^1C_4$ donor **9b** was activated at −30 °C under the aforementioned reaction conditions. At −20 °C a clean spectrum of a single species was observed (Figure 1b). A one-dimensional ^{1}H-TOCSY NMR spectra (Figure 1c) with irradiation of H2 and H4 revealed a major downfield shift of H1 ($\delta = 5.06$ ppm → $\delta =$ 7.46 ppm). Furthermore, a strong correlation between C1 and $H8_{ax}$ ($\delta = 4.23$ ppm), and to a minor extent with $H8_{eq}$ ($\delta =$ 4.82 ppm) in the ^{1}H-^{13}C-HMBC spectrum (Figure 1d) indicated formation of a ring system. The $^3J_{H1,H2}$ coupling constant of 6.0 Hz supports a diaxial orientation and suggests an α-sulfonium ion.

The observation of the β-sulfonium ion after activation of **9a** and the α-sulfonium ion found following activation of **9b** support the hypothesis that these intermediates are displaced by the alcohol to provide α- and β-mannosides, respectively.[12] However, glycosylation with the mannosyl donor **9c**

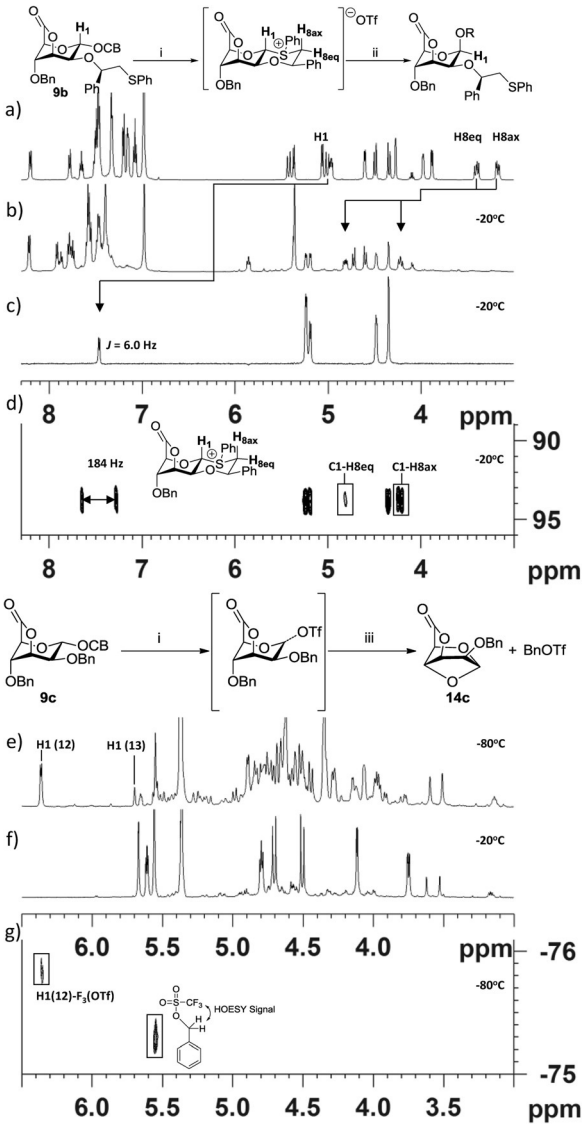
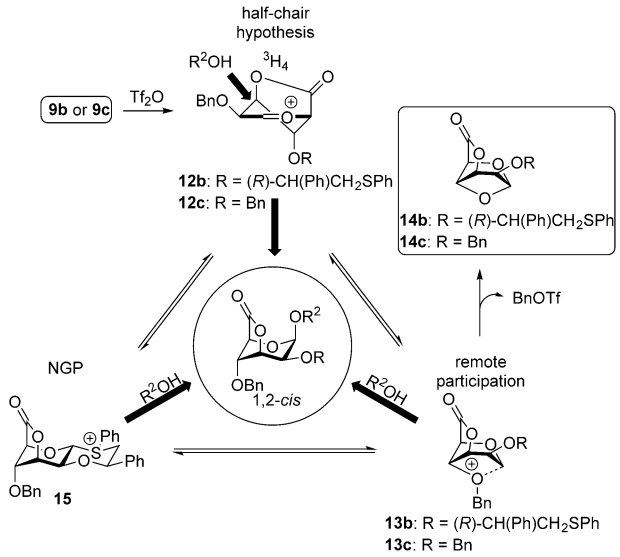


Figure 1. VT-NMR study of donors **9b**,**c**. Reaction conditions: i) 2.0 equiv DTBMP + 1.0 equiv Tf_2O; ii) **10** or **11**; iii) Raising temperature. a) **9b** pre-activation at −30 °C. b) Activated **9b** at −20 °C. c) ^{1}H-TOCSY spectrum of the activated **9b**. d) HMBC spectrum of **9b** post-activation. e) ^{1}H NMR spectrum of activated **9c** at −80 °C. f) H NMR spectrum of activated **9c** at −20 °C. g) ^{1}H-^{19}F HOESY spectrum of activated **9c**.

was also highly β-selective. Previously, high α-selectivity was observed in glycosylations with galacturonic acid lactones.[7] The selectivity was attributed to the disarmed nature of the acceptor although exemptions were reported in a later study.[14] The observed β-selectivity could also be explained by pseudoaxial attack on the $^3H_4$ oxocarbenium ion to provide the observed 1,2-*cis* addition.[15] Finally, anomeric triflate species may also be important intermediates.[16]

To investigate the reaction intermediates, **9c** was activated at −78 °C. A VT-NMR study at −78 °C showed a mixture of several species (Figure 1e). Close examination with ^{19}F-NMR spectroscopy (see the Supporting Information) showed triflated intermediates were present. ^{1}H-^{19}F-HOESY (Figure 1g) in combination with ^{1}H-^{13}C-HSQC and ^{1}H-^{13}C-HMBC spectra characterized these species as an anomeric triflate and to our surprise, benzyltriflate. To observe the stability of the triflate, the sample was heated gradually until one species remained at −20 °C (Figure 1f). Extensive NMR studies (see the Supporting Information) showed a strong H1–C4 correlation which, together with the formation of benzyl triflate, led us to conclude that the tricyclic compound **14c** had formed.

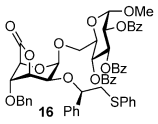
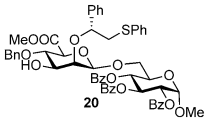
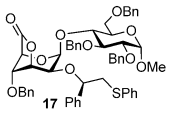
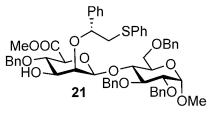
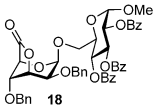
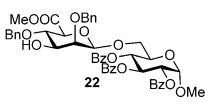
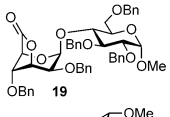
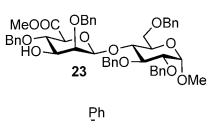
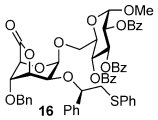
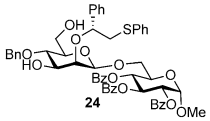
We propose that upon activation of **9c**, the intermediate oxocarbenium ion **12c** is stabilized by the C4 benzyl ether to form **13c** (Scheme 3). In the absence of the acceptor, this



Scheme 3. Proposed remote participation in the mannuronic acid lactones **9b** and **9c**.

intermediate ultimately results in the formation of **14c** and benzyl triflate. The formation of **14c** and benzyl triflate indicate NGP of the C4 benzyl group, and may also explain the high β-selectivity of **9b**.[17] Careful examination of the glycosylation mixture indeed showed the presence of **14c** as a side product in moderate quantities. A batch experiment to reproduce **14c** from **9c** was performed and gave **14c** in good yield (79%). Unlike earlier reported 1,4-anhydro sugars, the 1,4-anhydro-3,6-lactone **14c** was stable and neither polymerization nor furanose formation was observed.[18] In addition to remote participation of the C4 benzyl ether, the expected $^3H_4$ conformation of the oxocarbenium ion may also lead to the β-product.[15] In principle, although not observed in the NMR study at −20 °C, C4 benzyl participation could also occur in **9b** and indeed the tricyclic compound **14b** could be retrieved as a side product in the glycosylation reaction. The formation of **14b** as a side product may explain the moderate yields observed (Table 1, entries 1–4). Although **14b** is ultimately formed, VT-NMR experiments show that sulfonium ion formation is highly favored at −20 °C. Therefore, in case of **9b**, an additional pathway via the sulfonium ion **15** may lead to β-mannosides but the observed selectivity is more likely to be a result of the aforementioned alternative pathways.

Table 2: Opening of the dissaccharide lactones.

Entry	Lactone	Product	Yield [%][a]	$^1J_{C1\text{-}H1}$ [Hz]
1	 **16**	 **20**	90	156
2	 **17**	 **21**	91	155
3	 **18**	 **22**	89[b]	160
4	 **19**	 **23**	80	156
5	 **16**	 **24**	90	155

[a] Yield of isolated product. [b] An inseparable mixture with **14c.**

Finally, the opening of mannuronic acid lactones **16**–**19** with Dowex(H^+) in MeOH restored the conformation to $^4C_1$ and afforded the corresponding methyl esters **20**–**23** in high yield.[15b,19] The orientation of H1 was confirmed using the $^1J_{C1\text{-}H1}$ coupling constants, again confirming the 1,2-*cis* substitution (Table 2, entries 1–4).[13] Additionally, the mannuronic acid lactone **14** was selectively reduced to its corresponding mannose analogue using K-selectride to obtain **24** in 90% yield (entry 5).[20] This approach may be an attractive way to prepare β-mannosides found in the human core N-glycan.

In conclusion, we have shown that chiral auxiliaries can be used to prepare β-mannosides by NGP. To make *trans*-decalin sulfonium ion formation possible it is imperative to use $^1C_4$ mannosides. As a result of this conformation, the C4 benzyl substituent is also able to engage in remote NGP and provide 1,2-*cis*-mannosides. Although good alternatives for β-mannosylation are available, the method described herein relies on NGP, which is a generally applicable method. Hence, the use of NGP to prepare 1,2-*cis*-glycosides of gluco- and manno-type sugars is now possible, thus bringing us one step closer to a unified procedure for 1,2-*cis* glycosylation.

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Keywords: chiral auxiliaries · glycosylation · neighboring-group effects · stereoselectivity · sulfur

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