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# A novel approach towards the stereoselective synthesis of 2-azido-2-deoxy-β-D-mannosides

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**Abstract**—Low temperature mannosylation of glycosyl acceptors under the agency of *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT) and trifluoromethanesulfonic anhydride ($Tf_2O$) with *p*-methoxyphenyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside, readily available from D-mannosamine hydrochloride, affords 2-azido-2-deoxy-D-mannosides with high β-selectivity in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

In 1989, Kulaev et al.[1] reported that the bacteriolytic complex lysoamidase, isolated from a bacterium of the genus *Xanthomonas*, is highly efficient in combating external infectious diseases caused by Gram-positive bacteria. Structure analysis revealed[2] that the high molecular mass (1300 kDa) acidic polysaccharide **1** with the following trisaccharide repeating unit constitutes the main component of the bacteriolytic enzymatic preparation. It was also established[3] that the activity of lysoamidase is significantly stabilized by the interaction of the bacteriolytic enzymes,[4] which only amount to 2% of the total mass, with the acidic polysaccharide **1**. With the ultimate goal to study in depth the interaction of the lysoamidase enzymes with well-defined fragments of the linear polysaccharide **1**, we report here our preliminary results in preparing dimers containing an orthogonally protected 2-azido-2-deoxy-β-D-mannopyranosyl moiety, which will serve as a progenitor for the β-linked 2-acetamido-2-deoxy-D-mannuronic acid (β-D-Man*p*NAcA) unit in **1**.

**1**: →3)-β-D-Glc*p*NAc-(1→4)-β-D-Man*p*NAcA-(1→3)-α-L-Gal*p*NAcA-(1→
4
|
OAc

Of the methods thus far developed for the introduction of the β-ManNAc motif, the use of the 2-(benzoyloxyimino)-2-deoxy-α-D-*arabino*-hexapyranosyl bromide **2** (see Fig. 1) as a glycosyl donor[5,6] proved to be superior, in terms of easy accessibility and β-selectivity, to the originally proposed 2-azido-2-deoxy-α-D-mannopyranosyl bromides **3a**,**b**.[7] On the other hand, the methodology involving the *a posteriori* introduction of the azido function via $S_N2$-substitution at C-2 in β-linked glucosides[8] was very rewarding in the elaboration of the β-ManNAc element in the repeating unit of *Streptococcus pneumoniae* 19F capsular polysaccharide.[9,10]

Recently, Crich and Sun[11] attained a high β:α ratio and good yield of D-mannosides by activation of 2,3-di-*O*-alkyl-4,6-*O*-benzylidene-1-thio-α-D-mannosides **4a**,**b** at low temperature with in situ generated phenylsulfenyl

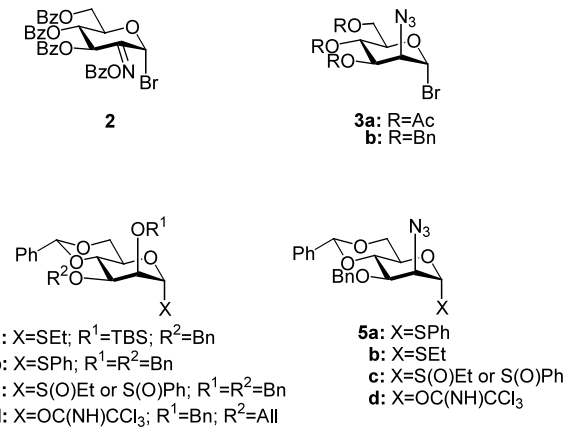


**Figure 1.**

*Keywords*: β-mannosidation; *p*-methoxyphenyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside; acidic polysaccharide.

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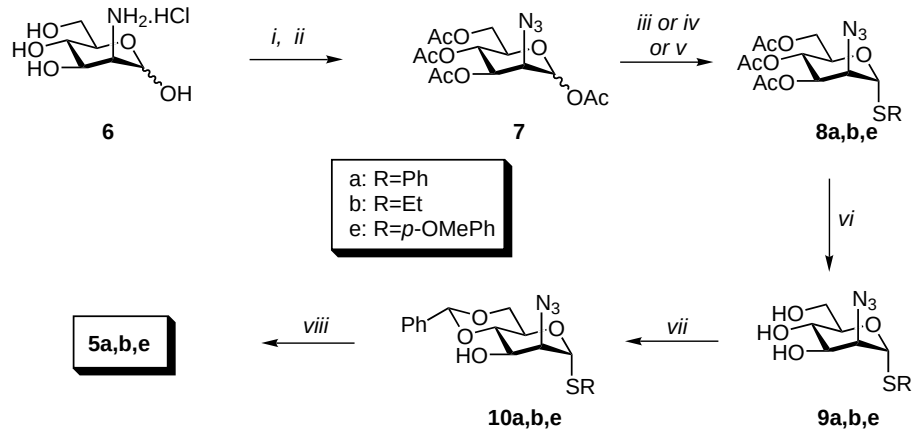
triflate (PhSOTf) and subsequent addition of glycosyl acceptors. The mannosidation protocol could be improved substantially[12] from a practical point of view using the combination of crystalline and stable *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT) and trifluoromethanesulfonic anhydride ($Tf_2O$), instead of PhSOTf, in the transformation of donors **4a**,**b** into the α-mannosyl triflates, which are proposed[11–13] to play a decisive role[14] in β-product formation. It was envisaged that condensation of the similarly protected ethyl-(phenyl) 2-azido-2-deoxy-1-thio-mannosides **5a**,**b** with glycosyl acceptors by the latter glycosidation approach would give access to 2-azido-2-deoxy-β-D-mannosides.

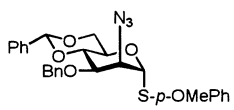
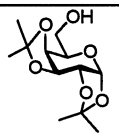
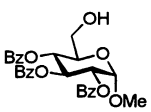
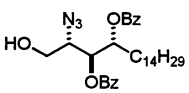
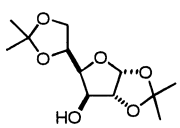
The synthesis of the requisite thiomannosides **5a**,**b** via a six-step sequence from commercially available D-mannosamine hydrochloride **6** is presented in Scheme 1. For example, subjection of **6** to diazo transfer reaction[15] and subsequent acetylation led to fully acetylated derivative **7** as a mixture of anomers. Treatment of **7** with ethanethiol in the presence of $BF_3{\cdot}OEt_2$ followed by deacetylation gave ethyl 1-thio-α-D-mannopyranoside **9b**. Acetalisation of **9b** with benzaldehyde dimethylacetal under the agency of $HBF_4{\cdot}OMe_2$ afforded, after benzylation, ethylthio donor **5b** in an overall yield of 50% based on **6**.

In the first instance, phenylthio donor **5a** in dry $CH_2Cl_2$ was activated for 5 min at −60°C with MBPT/$Tf_2O$ in the presence of 2,6-di-*tert*-butylpyridine (DTBMP). Addition of diacetone-D-galactose **11** and analysis of the mixture, after additional stirring for 10 min at −60°C,




**Scheme 1.** *Reagents and conditions*: (i) $TfN_3$, $K_2CO_3$, $CuSO_4$ (cat.), $H_2O$, MeOH, $CH_2Cl_2$; (ii) $Ac_2O$, DMAP (cat.), pyridine, **7**: 88% (two steps); (iii) EtSH, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 35°C, **8a**: 55%; (iv) PhSH, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 35°C, **8b**: 70%; (v) *p*-OMePhSH, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 35°C, **8e**: 59%; (vi) KO$^t$Bu, MeOH, **9a**/**b**/**e**: quant.; (vii) $PhCH(OMe)_2$, $HBF_4{\cdot}OMe_2$, DMF, **10a**: 88%, **10b**: 91%, **10e**: 88%; (viii) BnBr, NaH, DMF, **5a**: 96%, **5b**: 90%, **5e**: 97%.

**Table 1.** Mannopyranoside formation of 4,6-*O*-benzylidene protected donor **5e** with acceptors **11** to **14**

| Entry | Donor | Acceptor | Product | Yield (%)[a,b] | Ratio α:β[a] | $^1J_{C1,H1}$ (Hz) α-anomer | $^1J_{C1,H1}$ (Hz) β-anomer |
|---|---|---|---|---|---|---|---|
| 1 |  **5e** |  **11** | **15** | 83 | 1:2.1 | 169.4 | 160.2 |
| 2[c] | **5e** |  **12** | **16** | 87 | 1:4 | 171.2 | 159.5 |
| 3 | **5e** |  **13** | **17** | 59 | Only β | - | 160.2 |
| 4 | **5e** |  **14** | **18** | 61 | Only β | - | 158.0 |

[a]Total yield and α:β ratio were assigned after separation of the anomers. [b]Yield based on **5e**. [c]α:β ratio determined by $^1$H-NMR spectroscopy.

revealed the presence of starting materials and no trace of the expected coupling products. Moreover, executing the activation step at higher temperatures (−60→−20°C) or prolonged reaction times was also not successful. In addition, glycosidation at temperatures above −20°C led to intractable mixtures of products. Similar results were also obtained in subjecting the ethylthio donor **5b** to the same glycosidation conditions.

The failure of activating donors **5a**,**b** at low temperature can be explained[16] by taking into consideration that the nucleophilicity of the sulfur atom at the anomeric center will be decreased due to the electron withdrawing effect of the 2-azido group.[17] It was therefore, envisaged that replacement of the anomeric functions in **5a**,**b** by the more electron donating *p*-methoxyphenylthio group would have a beneficial effect on the activation step. Indeed, it turned out that activation of donor **5e**,[18] prepared in a similar fashion as **5a**,**b** (Scheme 1), for 15 min at −35°C followed by the addition at −60°C of diacetone-D-galactose **11**, led to the expected disaccharide **15** (entry 1 in Table 1)[19] as a mixture of anomers in good yield within 10 min. The stereochemistry of the mannosidic bond in the resulting individual anomers was firmly ascertained[20] on the basis of the C1–H1 heteronuclear one-bond coupling constants ($^1J_{C1,H1}$). An increase of β-selectivity was observed (entry 2) in the glycosylation of methyl 2,3,4-*O*-benzoyl-glucopyranoside **12** with **5e**. On the other hand, condensation of **5e** (entry 3) with the relatively more inert primary alcoholic function in the sphingosine derivative **13** led to the exclusive formation, although in moderate yield, of the 2-azido-2-deoxy-β-mannoside **17**. A similar result was observed (entry 4) in the glycosidation of **5e** with the secondary hydroxyl group in acceptor **14**. At this stage, it is also of interest to note that the stereochemistry and yield of the mannosidations summarized in Table 1 do not deviate substantially from those observed earlier by Crich and Smith using the corresponding α-D-thiomannoside **4b** as donor. However, the β-selectivity of the condensation of **5e** with acceptor **12** (entry 2) is less pronounced in comparison with the nearly exclusive formation of the β-mannoside resulting from the coupling of the corresponding partially acetylated glucose acceptor with phenyl α-D-thio-mannoside **4b**.

In conclusion, the results thus far obtained indicate that the readily accessible and orthogonally protected *p*-methoxy-phenyl 2-azido-2-deoxy-α-D-mannoside **5e** shows promise in the construction of the (1→3) *cis*-linked Man*p*NAcA structural element of the target molecule **1**. Moreover, in analogy with the earlier observed high β-mannoselectivity of the ethyl(phenyl) sulfoxide[11] **4c** and trichloroacetimidate[21] **4d** donors, it would also be of interest to examine the disarming effect of the 2-azido group on the low temperature activation of the corresponding 2-azido-2-deoxy donors **5c** and **5d**. Both aspects are currently under investigation and will be reported in due course.

## Acknowledgements

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18. All new compounds were fully characterized by $^1$H, $^{13}$C NMR and MS. Relevant data of donor **5e**: $^1$H NMR $\delta_H$ (200 MHz, $CDCl_3$): 7.58–7.30 (m, 12H), 6.86 (d, 2H, *J* 6.5 Hz), 5.63 (s, 1H), 5.26 (bs, 1H), 4.82 (AB, 2H), 4.35 (m, 1H), 4.20 (m, 4H), 3.82 (t, 1H, *J* 10.2 Hz), 3.77 (s, 3H). $^{13}$C NMR $\delta_C$ (50.1 MHz, $CDCl_3$): 160.19, 137.93, 137.51, 135.14, 129.01, 128.53, 128.26, 127.89, 127.65, 126.19, 122.77, 114.94, 101.60, 87.89, 79.25, 75.88, 73.34, 68.30, 65.03, 63.88, 55.23. MS (ESI): $m/z$=528.4 $(M+Na)^+$.
19. General experimental procedure for the preparation of 2-azido-2-deoxy-D-mannosides **15**–**18**: To a stirred solution of thiomannoside **5e** (0.20 mmol), MPBT (66 mg, 0.25 mmol), DTBMP (102 mg, 0.5 mmol) and activated 3 Å powdered molecular sieves in anhydrous dichloro-

methane (2.5 mL) at −35°C under argon was added $Tf_2O$ (70 μL; 0.4 mmol). After 15 min, the reaction mixture was cooled down to −60°C and subsequently a solution of the glycosyl acceptor (0.40 mmol) in anhydrous dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred for 10 min at −60°C and then quenched with methanol, warmed to room temperature, filtered, washed with saturated aqueous $NaHCO_3$, followed by brine, dried ($Na_2SO_4$) and concentrated under reduced pressure. The anomers where then separated, if appropriate, by silica gel chromatography (ethyl acetate/toluene).

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