Pergamon

Tetrahedron Letters 39 (1998) 1681–1684

TETRAHEDRON LETTERS

Direct Synthesis of β-D-Xyl-(1→2)-β-D-Man-(1→4)-α-D-Glc-OMe: a Trisaccharide Component of the *Hyriopsis schlegelii* Glycosphingolipid

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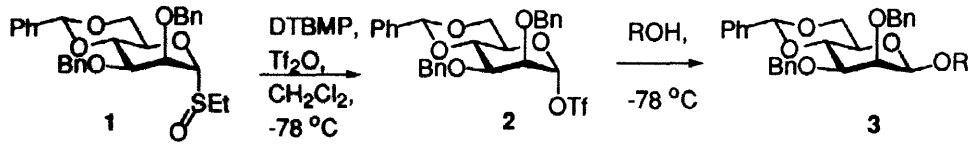
Received 17 September 1997; accepted 5 January 1998

Abstract. A synthesis of the target trisaccharide is described in which the key β-mannosylation is achieved in high yield and selectivity through reaction of the sulfoxide **7** with acceptor **8**, mediated with triflic anhydride. The β-xylosylation was best conducted using tribenzoyl xylopyranosyl bromide and silver triflate.

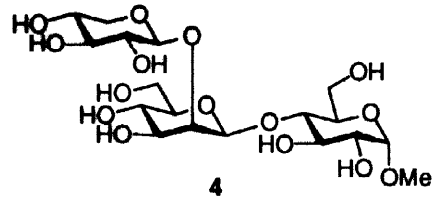
Recently, we described an efficient direct synthesis of β-mannopyranosides.[1,2] In this extension of Kahne's sulfoxide glycosylation strategy,[3,4] the glycosyl donor **1** is converted *in situ* to the triflate **2** by treatment with triflic anhydride (Tf_2O) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at -78 °C.[5] Addition of the acceptor then results in a clean S_N2-like displacement giving the β-mannoside **3** (Scheme 1).[5] At the present time, dichloromethane is the optimum solvent for this reaction and the 4,6-benzylidene protecting group is found to be essential for the achievement of high β:α ratios.[1,2]



Scheme 1

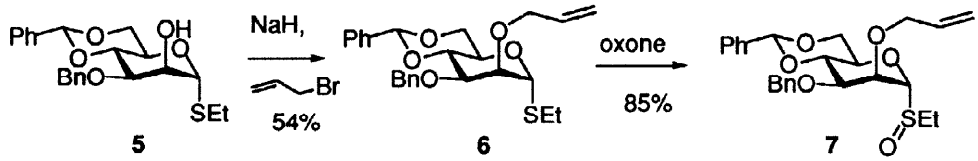
We now describe application of this protocol to the direct synthesis of β-D-Xyl-(1→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**4**), the methyl glycoside of a trisaccharide component of the *Hyriopsis schlegelii* glycosphingolipid.[6] We selected this target for a number of reasons. Firstly, the β-mannosylation step requires coupling to *O*-4 of a glucopyranose, one of the least reactive acceptors and so a true test of any glycosylation method.[7] Secondly, the target requires us to prepare and assess an equivalent to donor **1**, orthogonally protected at *O*-2 and *O*-3. Thirdly, trisaccharide **4** has been previously synthesized by Lichtenthaler[8] by his ulosyl bromide method,[9] and so provides the opportunity for a comparison of the two methods.

0040-4039/98/$19.00
PII: S0040-4039(98)00124-5



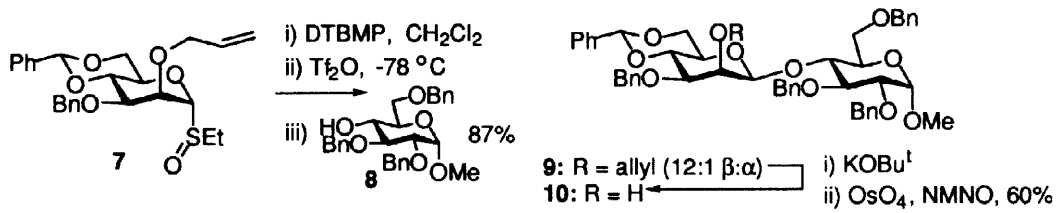
4

The differentially protected donor **7**[10] was readily prepared by reaction of **5**, itself available by selective *O*-3 monobenzylation of *S*-ethyl 4,6-di-*O*-benzylideneglucothiopyranoside via reaction of the dibutylstannylene acetal with benzyl bromide,[11] by reaction with sodium hydride and allyl bromide, then oxidation with oxone (Scheme 2). Interestingly, and as in the preparation of **1**, a single, unassigned diastereomer of the sulfoxide **7** was obtained.



Scheme 2

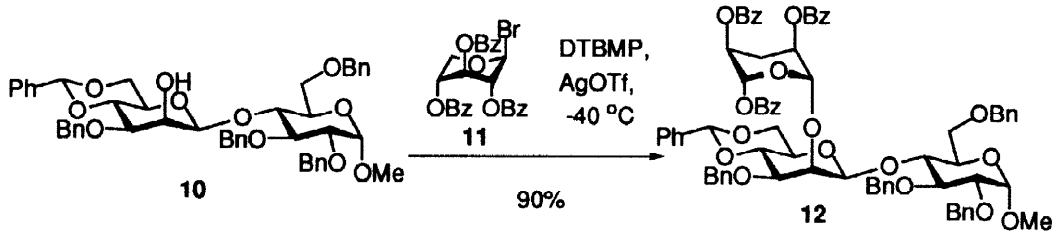
Sulfoxide **7** was subjected to our standard mannosylation conditions[2] using the acceptor **8**[12] when an 87% yield of disaccharide **9** was obtained in the form of a 12:1 β:α- mixture (Scheme 3). The configuration of the newly formed glycoside follows from the observation of an n.O.e correlation between H's 1 and 5 of the mannose ring, and additionally from the $^{1}J_{CH}$ coupling of 159.5 Hz for the mannose C1 in the proton coupled ^{13}C-NMR spectrum.[13] The allyl ether was then removed by isomerization with potassium *tert*-butoxide, followed by exposure to catalytic OsO_4 and *N*-methylmorpholine *N*-oxide (NMNO)[14] giving **10** in 60% yield (Scheme 3).



Scheme 3

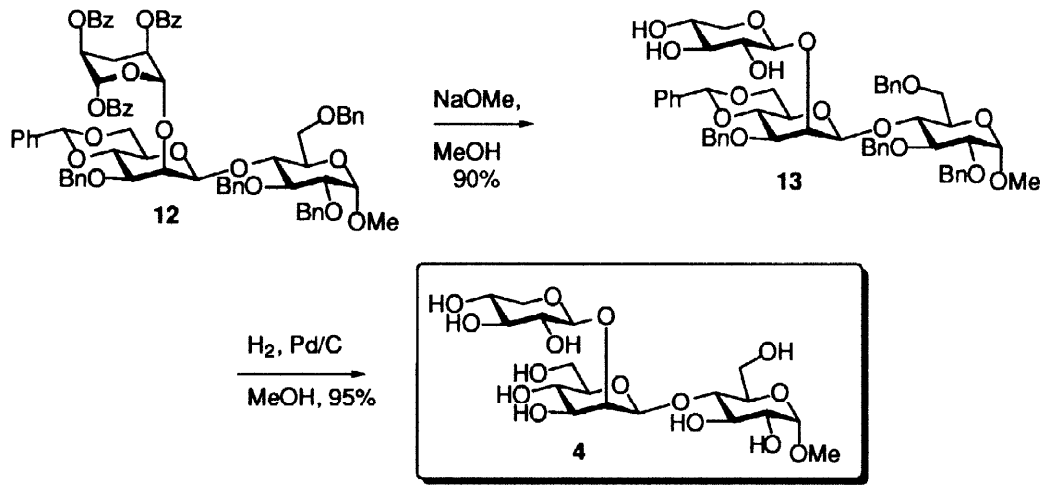
Xylosylation of **10** was best achieved under the conditions described by Lichtenthaler for a closely related substance.[8] Thus, a dichloromethane solution of **10**, the xylosyl bromide **11**,[15] and DTBMP was exposed at -40 °C to silver triflate resulting in the formation of the β-xylopyranoside **12** in 90% yield, as a single anomer (Scheme 4). In our hands this method was far superior to all other methods tried, including the

Schmidt trichloroacetimidate[16] and Kahne sulfoxide,[3,4] methods, for this particular coupling. The narrow unresolved multiplets observed in the ^{1}H-NMR spectrum of **12**, assigned to H's 1-4 of the xylose ring, are consistent only with a β-xylopyranose in the anticipated[17] $^1C_4$ conformation.



Scheme 4

Deprotection of **12** was achieved by a two step protocol. Firstly, the benzoate esters were removed by treatment at room temperature with catalytic NaOMe in methanol, giving a 90% yield of **13**. This step also occasions inversion of the xylose to the $^4C_1$ chair conformer indicated. This is change in conformation is not at all apparent from the complex ^{1}H-NMR spectrum, but is readily deduced from the ^{13}C-NMR spectrum, in $CDCl_3$, wherein there is a significant change in the chemical shift of the xylose anomeric carbon on going from **12** (δ 97.6) to **13** (δ 103.4). Finally, stirring of **13** in methanol over Pd/C for three days at room temperature under one atmosphere of hydrogen cleanly removed all remaining protecting groups and furnished the target molecule (**4**) in 95% isolated yield (Scheme 5). In our hands, **4** was a crystalline [m.p. 212 °C (MeOH)], analytically pure monhydrate whose ^{13}C-NMR spectrum and specific rotation {$[\alpha]_D^{20}$ = +20° (c = 0.1, water)} corresponded with those reported by Lichtenthaler for the same substance.[8]



Scheme 5

In summary, through the synthesis of **4**, we have demonstrated that our direct mannosylation functions efficiently for coupling to the weakly nucleophilic donor **8**. The yield, selectivity, and simplicity of

this method make it very comparable with the best of the recent methods for the preparation of β-mannopyranosides,[9,18-21] and very attractive for use in oligosaccharide synthesis. Such syntheses are underway and will be reported on in due course.

Acknowledgment. We thank the NSF (CHE 9625256) for partial support of this work.

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