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Synthesis of β-Mannopyranosides from α-Epimers by Radical Inversion. 1,6-Hydrogen Transfer Reactions of 2-*O*-(2-Bromoaryl)dimethylsilyl-α-methyl-D-mannopyranosides

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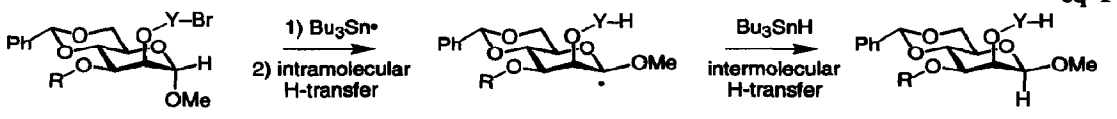
***Summary**: Intramolecular hydrogen transfer reactions of 3-O-acyl-α-methyl-D-mannopyranosides occur in a 1,6-fashion to give inverted β-mannopyranosides. The yields are limited by competing 1,5-hydrogen transfer reactions that give isomeric α-glucopyranosides.*

Stereoselective construction of the β-*O*-mannopyranoside linkage has received much attention in carbohydrate chemistry because this unit is a crucial component of the pentasaccharide core of N-linked glycoproteins.[1] The α-mannopyranoside bond is one of the easiest anomeric linkages to form, yet the β-mannopyranoside linkage is commonly considered to be the most difficult.[2] This suggests that a method to invert α-mannopyranosides to β would be especially useful. α-Mannopyranosides are generally more stable than their β-epimers, so thermodynamic inversions are not possible.

We hypothesized that α-mannosides could be inverted to β by a sequence of radical reactions involving first an intra- then an intermolecular hydrogen atom transfer, as summarized in eq 1. The successful outcome of the second (intermolecular) hydrogen transfer can be confidently predicted based on the studies of related anomeric radicals by Crich, Kahne, and others.[3] Intramolecular hydrogen transfer reactions are well known,[4] and we and others have recently introduced several functional groups, called "PRT" groups, that serve a dual purpose of protection and radical translocation.[5] Translocated radicals formed from these groups by 1,5-hydrogen abstraction have previously been used for inter- and intramolecular C–C bond-forming reactions,[5a-c] oxidations,[5d] and isotopic labelings.[5e] Appropriate PRT groups "Y" in eq 1 must serve to protect the mannose 2-OH group and to generate the translocated anomeric radical[4c-e] needed for inversion. In this Letter, we report studies directed towards the discovery of a suitable PRT group Y for the α to β mannose inversion. In validating the proposed inversion in eq 1, we have made the surprising discovery that groups based on 1,6-hydrogen transfer are superior to those based on 1,5-transfer. In the accompanying Letter, Crich and coworkers propose the same concept for inversion, encounter similar problems, and develop a different solution.[6]

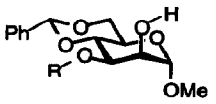
eq 1



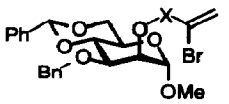
1 (α-manno) anomeric radical **2** (β-manno)

The substrates for this study were all prepared from the 3-*O*-benzyl- or 3-*O*-benzoyl-4,6-benzylidene α-methyl-D-mannopyranosides **3** or **4**.[7] We first tried an approach based on 1,5-hydrogen transfer reactions. Reduction of substrates like **5-7** at low, fixed tributyltin hydride concentrations

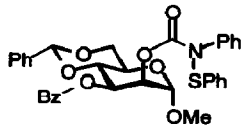
(0.05 M or lower) did not provide β-methyl mannopyranosides. In each case, the simple reduction product (Br or SPh replaced by H) was formed predominantly, implying that the 1,5-hydrogen transfer step had failed.



3 R = Bn
4 R = Bz



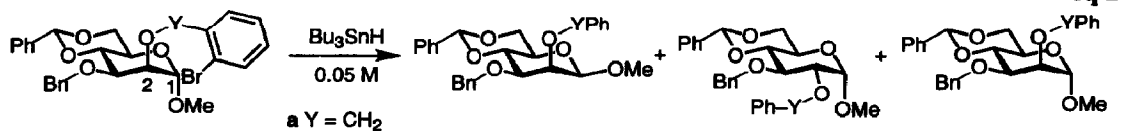
5 Y = CH_2
6 Y = $SiMe_2$



7

We next examined the possibility of inversion through 1,6-hydrogen transfer by using several of the groups that we had previously used for 1,5-hydrogen transfer.[5] About a half-dozen groups were surveyed in the 3-*O*-benzyl series, and the results from two representative examples are summarized in eq 2. In a standard procedure, an 0.05 M solution of **8a** or **8b** was heated for 14 h at 80°C with tributyltin hydride (1.3 equiv) and AIBN (0.1 equiv). After DBU/I_2 workup,[8] three products were easily separated by flash column chromatography, and their structures were determined by NMR spectroscopy and chemical correlation.[9] Reduction of *o*-bromobenzyl derivative **8a** provided two inverted products, the desired β-mannoside **9a** and α-glucoside **10a**, alongside the directly reduced product **11a** in a ratio of 21/13/65 (41% combined yield). The *o*-(bromophenyl)-dimethylsilyl ether **8b** provided the analogous three products **9b/10b/11b** in a ratio of 26/41/33 (58% combined yield).

eq 2



8a,b (a Y = CH_2, b Y = $SiMe_2$) — Bu_3SnH, 0.05 M — **9a,b** (β-manno) + **10a,b** (α-gluco) + **11a,b** (α-manno)

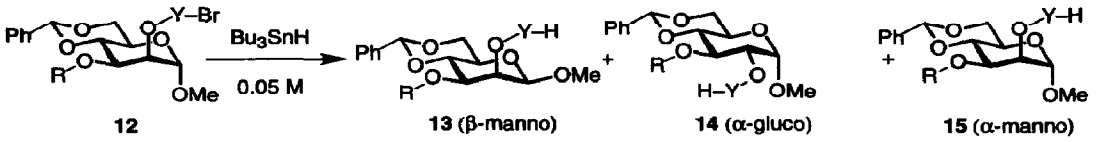
The β-mannose derivatives **9a,b** result from 1,6-H transfer followed by reduction of the anomeric radical with tin hydride (eq 1) while the α-glucose derivatives **10a,b** result from 1,5-H transfer followed by reduction of the resulting radical at C-2. Since both translocated radicals should be reduced with high facial selectivities,[3] the directly reduced products **11a,b** probably arise from bimolecular reduction of the aryl radical with tin hydride. Therefore, the amounts of **11a,b** could be reduced by decreasing the tin hydride concentration. The major problem is one of competing 1,5- versus 1,6-hydrogen transfer.

Changing the protecting group at C-3 from benzyl to acyl was next investigated. In this series of experiments, we surveyed only *o*-bromoaryldimethylsilyl translocating groups because they are easier to incorporate and remove than the *o*-bromobenzyl group and they gave better translocation (see eq 2). 3-Acyloxy-mannopyranosides **12a-g** were synthesized by selective acylation of methyl 4,6-*O*-benzylidene-mannopyranoside followed by silylation.[7] The inversions were carried out by the standard procedure described above, and the results are summarized in Table 1.

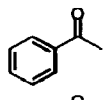
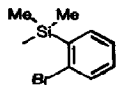
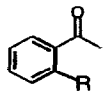
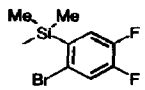
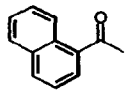
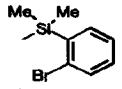
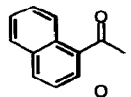
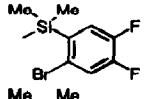
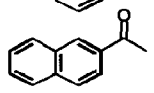
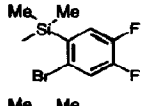
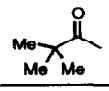
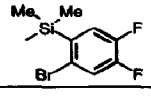
Compared to the 3-benzyl derivative **8b** (eq 2), the 3-acyl derivatives shown in Table 1 provide increased total amounts of radical translocation products (β-manno + α-gluco). Benzyl ether **8b** provides 67% translocated products (**9b** + **10b**) while acyl derivatives **12a-g** provide ≥72% translocated products (**13** + **14**). For some combinations of translocating and protecting groups (entries b and f), all the products result from radical translocation. In addition, there is a clear trend

favoring 1,6- over 1,5-hydrogen transfer. For the benzyl ether **8b**, the β-manno/α-gluco (**9b/10b**, 1,6-H/1,5-H transfer) ratio is 0.6, while acyl derivatives have ratios of **13/14** ranging from 1-2. Combined isolated yields of products range from 60-82%.

Table 1. Translocation Reactions of 3-*O*-Acyl-2-*O*-silyl-α-methyl-D-mannopyranosides 12a-f



12 **13** (β-manno) **14** (α-gluco) **15** (α-manno)

entry	R	Y–Br		β-manno : α-gluco : α-manno ratio[a]	yield,[b] %
a				48 : 24 : 28	68
b			R = H	50 : 50 : 0	82
c			R = F	52 : 37 : 11	72
d				47 : 31 : 15	63[c]
e				51 : 31 : 18	65
f				58 : 42 : 0	68
g				53 : 33 : 14	75

[a]Determined by ^{1}H NMR. [b]Total isolated yield. [c]Starting material was recovered in 7% yield.

These preliminary results validate the notion that anomeric inversion of α-mannopyranosides to β by a radical translocation strategy is possible, and isolated yields in the vicinity of 40% can be expected for the best current combinations of sugar protecting and radical translocating groups. The rate and regioselectivity of the hydrogen transfer reaction is clearly sensitive to the nature of these groups, so further variations may reveal improved combinations. When viewed in the larger picture,[4a] these intramolecular hydrogen transfer reactions are not especially fast. For abstraction of the anomeric hydrogen, the favorable radical stabilization effect on the product provided by the two oxygen substituents is largely offset by the anomeric effect, which stabilizes the ground state of the precursor.[4a] While modest rates for hydrogen transfer were expected, we were surprised to learn that 1,6-hydrogen transfers of the anomeric hydrogen were considerably faster than related 1,5-hydrogen transfers. Both this fact and the variability of the ratios as a function of substituents emphasize the importance of geometry in hydrogen transfer reactions of vinyl and aryl radicals.[4a]

The rates of 1,6-hydrogen transfer in Table 1 are already in an acceptable range, and the main problem with this strategy is now regioselectivity (1,6- versus 1,5-H transfer). The work of Crich and coworkers shows that strategies based on 1,5-hydrogen transfer are also viable with a class of translocating group based on alkyl radicals.[6]

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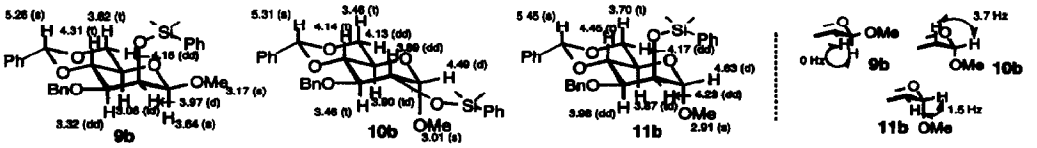
9. Configurations of the products were assigned from the ^{1}H NMR (300 MHz) spectra recorded in benzene-d_6. The data for **9b**, **10b**, and **11b** are representative of the other β-manno, α-gluco, and α-manno products.



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