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# Convenient Synthesis of Oxo-Linked 5a-Carba-di- and tri-saccharides of Biological Interests

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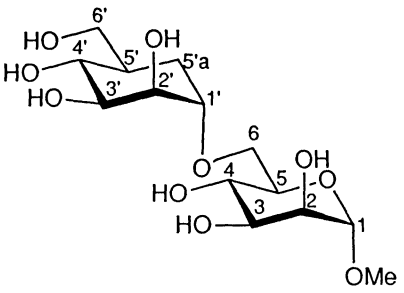
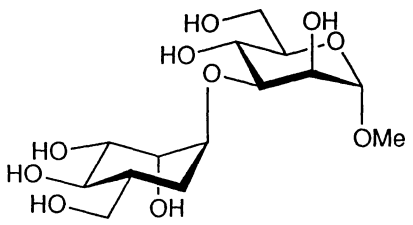
Some oxo-linked 5a-carba-di- and tri-saccharides of biological interests, including 5a-carbamaltose, were synthesized by coupling of 5a-carba-glycosyl donor, 1,2-anhydro-5a-carba-β-D-mannopyranose derivative with the alkoxides generated from the protected hexopyranose derivatives in *N,N*-dimethylformamide in the presence of a crown ether.

Carba-sugar[1] analogs of naturally occurring oligosaccharides of biological interests have so far been utilized as model compounds[2] for conformational analyses of true oligosaccharides, as substrates analog[3] for study of enzymatic actions, or as potent inhibitors[4] against sugar hydrolases.

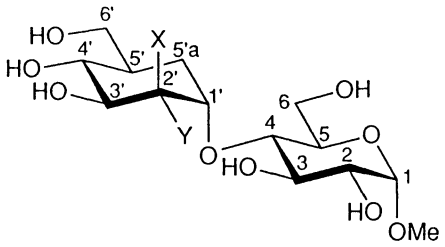
In a previous paper, we described a syntheses of 5a-carba-trehaloses,[5] -maltoses,[6] -cellobioses,[6] -laminarabioses,[6] and of 5a-carba-trisaccharide analog[7] of the common branching trisaccharide, 3,6-di-*O*-(α-D-mannopyranosyl)-D-mannopyranose, occurring in glycoconjugates. These 5a-carba-analogs are all glycosides, namely, the non-reducing ends being comprised of true sugar residues. On the other hand, Paulsen *et al.*[8] reported the first synthesis of four oxo-linked 5a-carba-disaccharides mainly related to naturally occurring disaccharides by substitution of the 4- and 6-triflate derivatives of hexopyranoses with the protected 5a-carba-sugars. However, it may not be always easy to prepare appropriate triflate derivatives, being both stable and reactive toward desired nucleophiles.



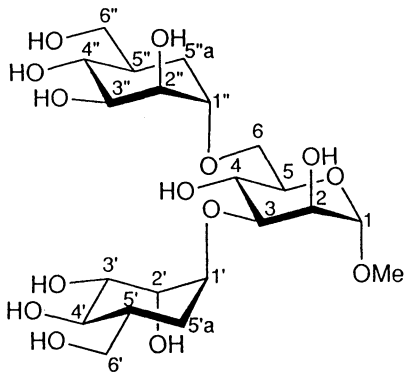

**1**
**1a :** heptaacetate




**2**
**2a:** heptaacetate



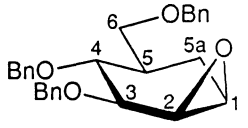
**3:** X = OH, Y = H
**3a:** heptaacetate
**4:** X = H, Y = OH
**4a:** heptaacetate



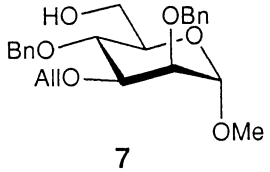
**5**
**5a:** decaacetate

We then envisaged a practical route to an oxo-linked 5a-carba-oligosaccharide by elaborating a simple 5a-carba-glycosyl donor readily acceptable by a protected hexopyranose or 5a-carba-hexopyranose derivative, and reported herewith a synthesis of 5a-carba-di- **1**—**4** and trisaccharide analogs **5** by employing 1,2-anhydro-3,4,6-tri-*O*-benzyl-5a-carba-β-D-mannopyranose[9,10] (**6**) as a donor.

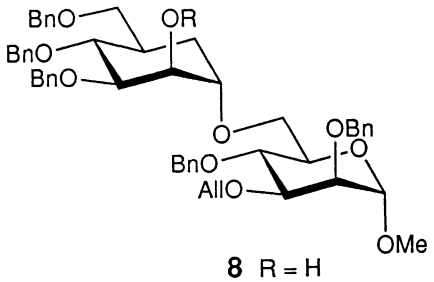
Initially, a Lewis acid-catalyzed reaction was attempted for construction of an ether linkage. Coupling of molar equivalents of **6** and methyl 3-*O*-allyl-2,4-di-*O*-benzyl-α-D-mannopyranoside[11] (**7**) in $CH_2Cl_2$ in the presence of trifluoroborane (-15 → 0 °C) gave a 37% yield of the protected 5a-carba-disaccharide **8**, together with **7** (58%) unchanged. The structure of **8** was assigned by converting it into the acetate **9**: $^1$H NMR spectrum[12] δ 5.58 (t, *J* 2.9 Hz, H-2') and 3.65 (q, *J* 2.9 Hz, H-1'). Compound **9** was de-*O*-allylated ($SeO_2$, AcOH/dioxane) and then hydrogenolyzed with Pd-C followed by acetylation, giving the heptaacetate **1a** (67% over-all yield), which was treated with methanolic sodium methoxide to afford **1**, $[\alpha]_D$ +47° (*c* 0.25, MeOH), quantitatively.



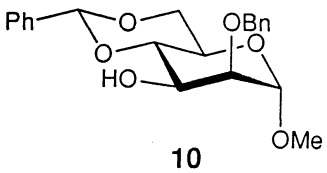
**6**



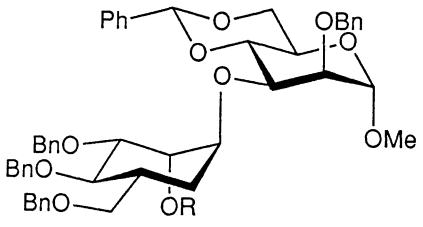
**7**



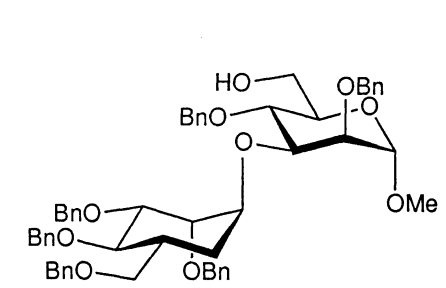
**8** R = H
**9** R = Ac



**10**



**11** R = H
**12** R = Ac
**13** R = Bn

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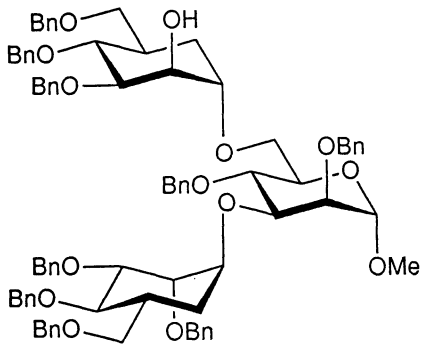
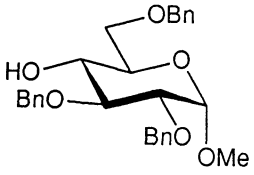



15

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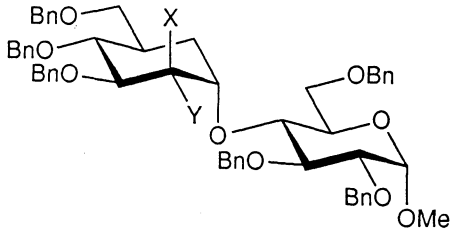


**17** X = OH, Y = H
**18** X = OAc, Y = H
**19** X = H, Y = OH
**20** X = H, Y = OAc

However, similar reaction of **6** with methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[13] (**10**) did not work. Hence the alcohol was first converted into the alkoxide with sodium hydride and then it was subjected to coupling with **6**. Thus, compound **10** was treated with large excess (15 molar equiv.) of NaH in *N,N*-dimethylformamide (DMF) at 0 °C under argon atmosphere, and then excess (2.8 molar equiv.) of **6** was added and the mixture was heated for 4 d at 70 °C. The coupling product **11** was obtained in 35% yield, and 48% of **10** was recovered. But, when 15-crown-5 ether (15 molar equiv.) was first added[14] to the reaction mixture, the yield of **11** was rather improved to 64%, **10** (27%) being recovered. The structure of **11** was assigned by converting it into the acetate **12**: $^1$H NMR spectrum[12] δ 5.57 (t, *J* 4.0 Hz, H-2'). Compound **12** was similarly converted *via* the heptaacetate **2a** to the free 5a-carba-disaccharide **2**, $[\alpha]_D$ +15° (*c* 0.07, MeOH).

Furthermore, compound **11** was transformed into the penta-*O*-benzyl ether **13**, the benzylidene group of which was then reduced with DIBAL-H in $CH_2Cl_2$ at room temperature to give mainly the 6-OH unprotected derivative **14**. Introduction of 5a-carba-mannopyranosyl residue was conducted by a similar treatment (2 d, 70 °C) with excess (3 molar equiv.) of **6** to give the 5a-carba-trisaccharide derivative **15** in 44% yield. De-*O*-benzylation of **15** was effected by hydrogenolysis with Pd black in EtOH and the product was isolated as the per-*O*-acetyl derivative **5a** (82% over-all yield), the structure of which was fully supported by the $^1$H NMR spectrum:[12] δ 5.39 (t, *J* 2.9 Hz, H-2''), 5.31 (t, *J* 3.3 Hz, H-2'), 3.73 (q, *J* 2.9 Hz, H-1''), and 3.62 (m, H-1'). Zemplén de-*O*-acetylation of **5a** gave the 5a-carba-trisaccharide **5**, $[\alpha]_D$ +7.1° (*c* 0.46, MeOH), quantitatively. It is the first example of an oxo-linked 5a-carba-trisaccharide, which as well as **1** and **2**, from a synthetic standpoint, would be a key building block for further elaboration of carba-oligosaccharides of biological interests.

In order to know further versatility of **6**, its coupling with a molar equivalent of methyl 2,3,6-

tri-*O*-benzyl-α-D-glucopyranoside[15] (**16**) was conducted under similar conditions. After 4 h at 70 °C when all **6** had been consumed, 45% of the coupling product **17** was isolated together with **16** (46%) being unchanged. The structure of **17** was assigned by converting it into the acetate **18** (82%): $^1$H NMR spectrum[12] δ 5.56 (t, *J* 2.5 Hz, H-2') and 4.09 (q, *J* 2.5 Hz, H-1'). The 2'-OH of **17** was oxidized with PCC in $CH_2Cl_2$ and successively reduced with $NaBH_4$ in MeOH in the presence of $CeCl_3$, affording **17** (38%) and the 2'-epimer **19** (45%). Compound **19** was the 5a-carbamaltose derivative and characterized as the acetate **20**: $^1$H NMR spectrum[12] δ 4.92 (dd, *J* 2.9 and 10.2 Hz, H-2') and 3.85 (t, *J* 10.2 Hz, H-3'). Compounds **18** and **20** were readily hydrogenolyzed with Pd-C to give the 5a-carba-disaccharides **3**, $[\alpha]_D$ +104° (*c* 0.34, MeOH), and **4**, $[\alpha]_D$ +127° (*c* 0.20, MeOH), in good yields.

Compound **6** was shown to be a versatile 5a-carba-hexopyranosyl donor, which reacts in DMF in the presence of a crown ether with the alkoxides generated from the sugar derivatives, affording in acceptable yields, the oxo-linked 5a-carba-di- and trisaccharides containing 5a-carba-α-D-mannopyranosyl residues. The *manno*-configuration of the 5a-carba-sugar residue was convertible to the *gluco*-configuration *via* the 2-keto compound, which would also be an intermediate to the 2-amino-2-deoxy congeners and like. Further improvement of the reaction conditions for construction of an ether linkage, as well as biological assay and conformational analysis of 5a-carba-di- and trisaccharides prepared in this study are under way.

References

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