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Synthesis of D-rubranitrose by using a novel method for constructing functionalized branched-chain structures

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Abstract—Convenient synthesis of D-rubranitrose from D-glucose was achieved by using simple and novel methods for deoxygenation and construction of functionalized branched-chain structures. The total yield of D-rubranitrose from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) was 4.9%.

D-Rubranitrose[1] and D-tetronitrose (kijanose[2]) (Fig. 1) belong to a family of 2,3,6-trideoxy-3-*C*-methyl-3-nitrohexose and have the same D-*xylo* configuration. The only difference is the substituent at C-4, that is, methoxy for the former and methoxycarbonylamino for the latter. These branched-chain sugars are a component of antibiotics. It is known that many antibiotics contain amino or branched-chain sugars in their molecule and that their bioactivity changes dramatically by a modification of the sugar portion.[3] Therefore the sugar modification suggests to be a very powerful tool, not only for elucidating their function but also for creating new medicines. In this paper, D-rubranitrose, a typical branched-chain sugar having a nitrogen at the branching point, was synthesized from D-glucose via the corresponding hexopyranosid-3-ulose with the D-*threo* configuration. Through this work, we would like to display some merits of our synthetic methods for extending the field of branched-chain sugars chemistry.

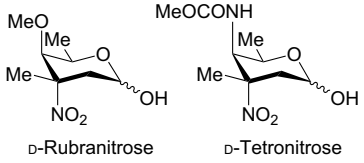

Figure 1.

Hitherto, Sato and co-workers synthesized D-evernitrose,[4] L-evernitrose,[4,5] *epi*-evernitrose,[5] L-rubranitrose,[6] D-rubranitrose,[7] methyl α-D-tetronitroside,[7] and a branched-chain amino sugar of antibiotic A35512B[8] by using cyanomesylation of the corresponding parent glycosidulose, followed by reductive spiroaziridine formation and reductive ring opening to a methyl-branched amino sugar, and finally oxidation to the nitro sugar. Using this method other research groups also succeeded in the synthesis of such branched-chain sugars[9] including L-vancosamine.[10] The other methods were also described on the synthesis of 2,3,6-trideoxy-3-amino- and 2,3,6-trideoxy-3-nitrohexoses involving the transformation of allylic alcohols to *cis*-1,2-amino alcohols[11] or the stereoselective C-alkylation of the corresponding α-amino carbonyl derivative.[12] However these methods are not satisfying for constructing the branched chain with the desired stereochemistry. In connection with this works, novel construction methods[13,14] for functionalized branched-chain structures with desired stereochemistry as well as practical deoxygenation methods under mild conditions[15] have been developed in our laboratory. Then, we have planed and achieved the synthesis of D-rubranitrose by using these practical methods as follows.

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**)[16] was treated with 3.0 equiv of methanesulfonyl chloride in pyridine to give the corresponding 2,3-di-*O*-mesyl derivative **2** in 98% yield. The compound **2** was derived

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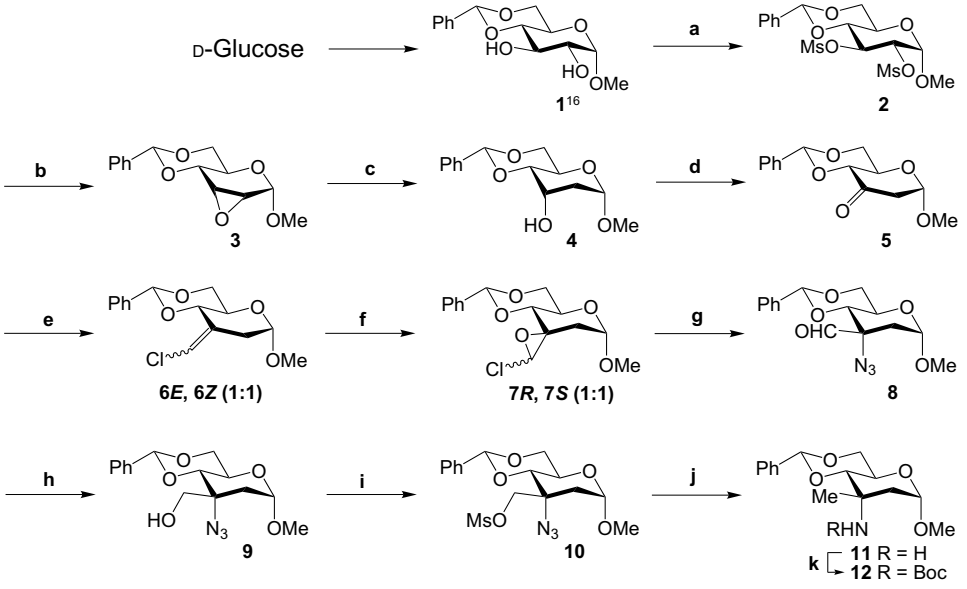
into *allo*-epoxide **3** in 78% yield by treatment with KOH in THF/MeOH (2:3 v/v) under reflux conditions for 3 h. Deoxygenation of **3** was achieved with $NaBH_4$ in DMSO[15] at 80 °C for 2.5 h to give 2-deoxy derivative **4** in 95% yield. This method may be useful for large-scale synthesis. Swern oxidation[17] of **4** gave the corresponding ulose **5** in 80% yield. Wittig reaction of **5** with Ph_3PCH_2ClI and *n*-BuLi in THF at −20 °C under argon gave the corresponding chloroolefins (**6***E*: mp 155–156 °C; **6***Z*: mp 146–147 °C; 1:1 mixture) in 81% yield. The configurations of **6***E* and **6***Z* were determined by NMR (NOESY: H-4 and olefin proton). A mixture of these diastereomers was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) in 1,2-dichloroethane at 70 °C for 6 h to give a *R*,*S*-mixture (1:1) of spiro α-chloroepoxide **7** (*R*-isomer at C-3′: mp 111–112 °C; *S*-isomer at C-3′: mp 89–91 °C) in 76% yield. The configurations of **7***R* and **7***S* at C-3 were supported by converting them into the same known unsubstituted *arabino*-spiroepoxide[18] by reduction of chlorine with *n*-Bu_3SnH/AIBN in toluene at 100 °C. A solution of the mixture of **7***R* and **7***S*, NaN_3 (5 equiv), and Me_4NCl (5 equiv) in DMF was stirred at 80 °C for 4 h to give the corresponding α-azidoaldehyde derivative **8** (mp 101–102 °C) in 82% yield and polar decomposition remainings. The reaction proceeded regioselectively.[13] The configuration of **8** at C-3 was determined by NMR (NOE: H-2 and CHO, 5.5%; H-4 and CHO, 5.5%). Then the quantitative and selective reduction of **8** by using $NaBH_4$ in H_2O–EtOAc gave hydroxymethyl derivative **9** (mp 129–130 °C), which was converted into the corresponding mesylate **10** (mp 124–125 °C) in 92% yield by using MsCl/Py. The compound **10** was reduced with $NaBH_4$ in DMSO[15] at 80 °C for 8 h to give methyl branched-chain amino derivative **11**, which was then derived into a syrupy butoxycarbonylamino derivative **12** (70% yield in two steps) (Scheme 1). This result suggests that reduction of the methanesulfonyloxymethyl group occurs first to give the methyl branched-chain derivative **A**, followed by the reduction of the azide group into the amino group, because, the reductive ring opening of the spiroaziridine derivative **B**, which was produced by catalytic reduc-



Scheme 1. Reagents and conditions: (a) MsCl/Py (98%); (b) KOH/THF–MeOH (78%); (c) $NaBH_4$/DMSO (95%); (d) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2 (80%); (e) Ph_3PCH_2ClI, *n*-BuLi/THF (81%, diastereomer ratio = 1:1); (f) *m*-CPBA/$(CH_2Cl)_2$ (76%); (g) NaN_3, Me_4NCl/DMF (82%); (h) $NaBH_4/H_2O$–EtOAc (quant); (i) MsCl/Py (92%); (j) $NaBH_4$/DMSO; (k) $(Boc)_2O$, Et_3N/THF (70% in two steps).

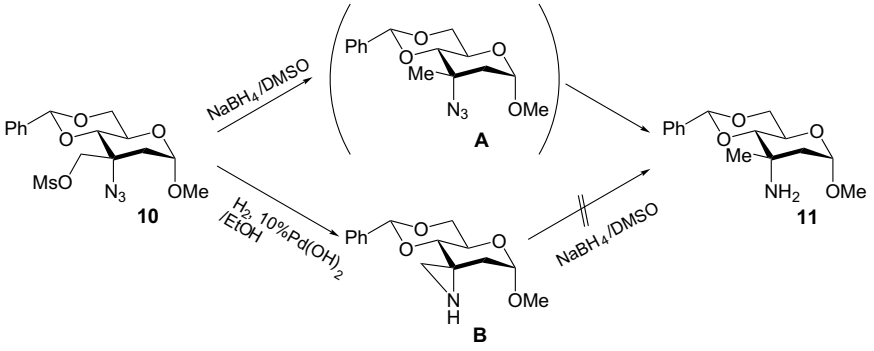
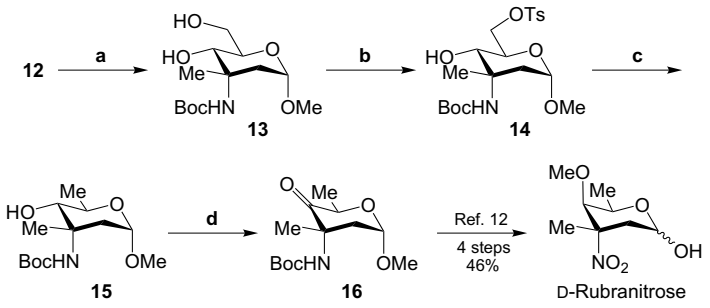


Figure 2. Proposed reaction mechanism of deoxygenation and reduction of compound **10**.



Scheme 2. Reagents and conditions: (a) 95% AcOH aq (93%); (b) TsCl/Py (90%); (c) $NaBH_4$/DMSO (89%); (d) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2 (76%).

tion of the methanesulfonyloxymethyl branched-chain amino derivative,[19] did not occur under these reaction conditions (Fig. 2). Usually the reductive ring opening of the aziridine ring is achieved under more drastic condition, for example, using an autoclave. Therefore this method for constructing methyl branched-chain amine structure should be very useful for large-scale synthesis. Interestingly, in the case of the 3-epimer of **10** having the axial methanesulfonyloxymethyl branched chain and the equatorial azide group, the same reaction conditions did not give the corresponding methyl branched-chain amino derivative but a spiroaziridine derivative.[19] The branched-chain compound **12** was then hydrolyzed with 95% AcOH aq for 48 h to give the deprotected diol **13** (syrup) in 93% yield. A selective tosylation of **13** with TsCl in pyridine at rt gave the corresponding 6-*O*-tosylate **14** (syrup) in 90% yield. The compound **14** was derived into the corresponding 6-deoxy derivative **15** (syrup) in 89% yield by $NaBH_4$/DMSO.[15] Then, Swern oxidation[17] of **15** gave the known carbonyl compound **16**[12] in 76% yield (Scheme 2). The physical constants of **16** were completely identical with that reported.[12] The further transformation of **16** into D-rubranitrose has been reported by Klemer and Wilbers[12] in 1987. As a result the synthesis of D-rubranitrose in 22 steps was successfully and conveniently accomplished. The overall yield from **1** was 4.9%.

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