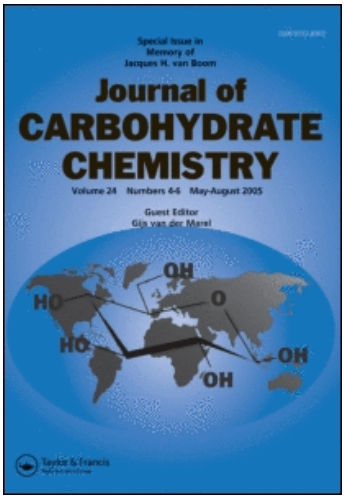

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Communication

SYNTHESIS OF METHYL α-D-KIJANOSIDE

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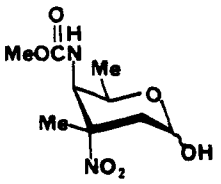
In 1981, Mallams and coworkers reported[1] the discovery of D-kijanose **1**, a branched-chain nitro sugar, isolated from the antitumor antibiotic kijanimicin by acid hydrolysis. The structure of this unusual carbohydrate was established[1,2] as 2,3,4,6-tetradeoxy-4-(methoxycarbonylamino)-3-C-methyl-3-nitro-D-xylo-hexopyranose by spectroscopic and crystallographic analysis, and comparison with D-rubranitrose **2**, a carbohydrate found in the antibiotic rubradirin.[3] Two other nitro sugars, L-evernitrose **3**[4] and L-decilonitrose **4**[5], have been discovered as components of antibiotics.



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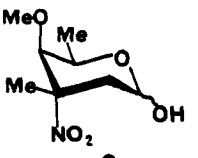

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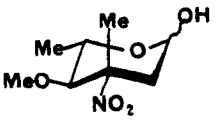

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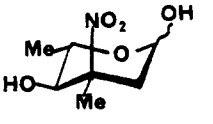

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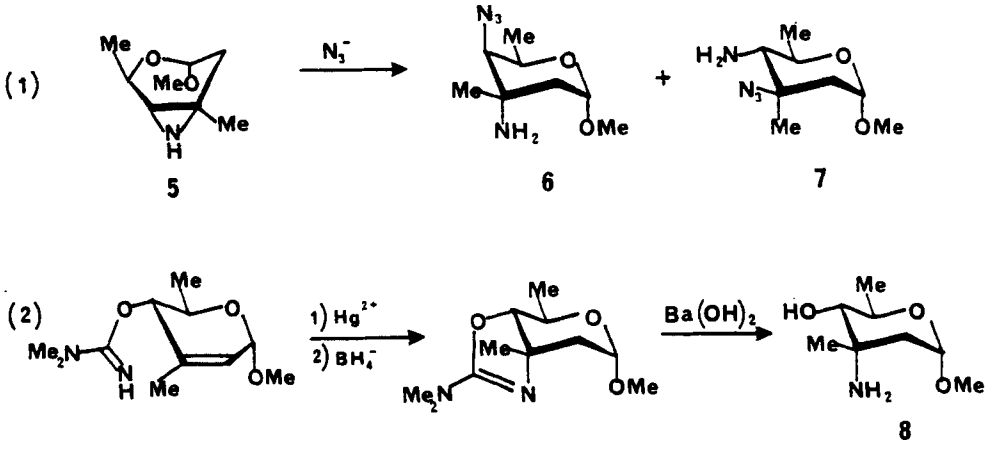
A critical problem in the synthesis of branched-chain nitro sugars is the introduction of the C-3 methyl and nitro groups with stereocontrol, and the synthesis of kijanose is further complicated by the carbamoyl group at C-4. The first synthesis of

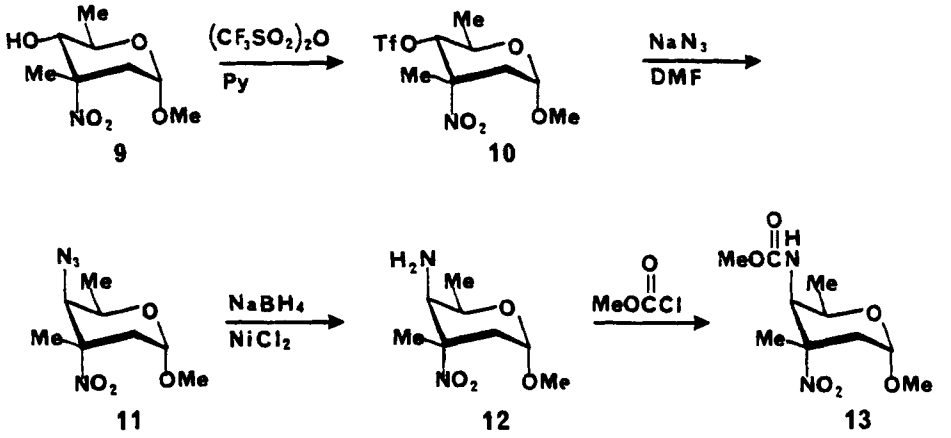
methyl α-D-kijanoside (**13**), reported[6] by Yoshii and coworkers in 1982, and the synthesis of **13** described recently[7] by Brimacombe and Rahman converge at aziridine **5** which undergoes azidolysis to give a mixture of isomers **6** and **7** in ratios of 4.5 : 1[7] and 3 : 2[6] in favor of the desired **6** (Eq. 1). We have recently developed[8] an efficient synthesis of amino alcohol **8** which was based on the cyclization of an imidate derived from dimethylcyanamide (Eq. 2). This sequence establishes the tertiary center at C-3 with complete regio and stereocontrol. We proposed that synthesis of both rubranitrose and kijanose could be developed from **8**, and herein we describe a stereospecific route to methyl α-D-kijanoside (**13**) via nitro alcohol **9**.



In nearly all of the existing routes to nitro sugars, oxidation of an amino group to a nitro group is carried out as the final step. In the synthesis of kijanose, such placement of the oxidation requires that the C-3 amino group be protected to allow for independent manipulation of the azido group at C-4. We felt that an efficient route to **13** which avoids protection-deprotection of the C-3 functionality could be developed from **9**, and that the electron-withdrawing properties of the nitro group might facilitate the introduction, by nucleophilic displacement, of nitrogen at C-4. Nitro alcohol **9**[8] was obtained from amine **8** by oxidation

with either m-chloroperbenzoic acid or ozone-silica gel.[9] The use of the latter reagent in nitro sugar synthesis has not been reported and, in the case of **8**, ozonation gave higher yields of the desired nitro alcohol. The procedure consists of passing ozone (Welsbach generator) through a sample of the amino alcohol adsorbed onto silica gel (dry; 10 g per 100 mg amine) at -78°C. Crystalline nitro alcohol was obtained in 80% yield by elution with 1:1 ethyl acetate-petroleum ether and evaporation.

Nucleophilic displacement reactions difficult to carry out in carbohydrates have been achieved with the use of highly reactive leaving groups such as trifluoromethanesulfonates[10] and imidazolylsulfonates.[11] Triflate **10** was prepared in quantitative yield by treatment of **9** with triflic anhydride in pyridine (Scheme 1). When **10** was treated with sodium azide in DMF at room temperature, axial azide **11**{$[\alpha]_D^{20}$ + 191°(c 0.12, chloroform); IR (film) 2109 (N_3), 1539 and 1348 (NO_2); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 4.68 (1, d, H-1, $J_{1,2a}$ = 4 Hz), 4.29 (1, q, H-5, $J_{4,5}$ = 1.3 Hz, $J_{5,6}$ = 6 Hz), 4.02 (1, bs, H-4), 3.23 (3, s, 1-OCH_3), 2.71 (1, d, H-2e, $J_{2a,2e}$ = 15 Hz), 1.96 (1, dd, H-2a), 1.68 (3, s, 3-CH_3), 1.39 (3, d, H-6); MS (CI, NH_3) m/e (rel. intensity) $(M+NH_4)^+$ at 248 (3), 216(10), 152(100)}, was obtained as a syrup in 82% yield. The axial orientation of the azido group in **11** was evident from the ^{1}H-NMR spectrum which displayed a coupling constant of 1.3 Hz for $J_{4,5}$. A value of 9 Hz is observed for the larger trans diaxial coupling of H-4 and H-5 in nitro alcohol **9**. Products resulting from ring-opening or elimination were not detected in the reaction product; however, when the reaction was conducted at 120°C for 1h, a lower yield (70%) of azide was obtained. Reduction of **11** to amine **12** was carried out with sodium borohydride in the presence of nickel (II) chloride[12] in ethanol (2 eq of $NaBH_4$ and $NiCl_2$, 43% yield). It was necessary to add the nickel chloride slowly to a stirred solution of **11** (reverse order) to avoid over-reduction. Higher yields (82%) of **12** were obtained when the crude reaction product was recycled in the reduction with one equivalent each of sodium borohydride and nickel chloride. Treat-



SCHEME 1

ment of the crude reaction product with methyl chloroformate gave methyl α-D-kijanoside (**13**) in 53% yield. Synthetic **13** was compared to a sample of methyl α-D-kijanoside obtained from the hydrolysate of kijanimicin[13] and found to have identical NMR (^{1}H and ^{13}C) and infrared spectra, optical rotation, and R_f (TLC) in different solvent systems.

This approach to branched-chain nitro sugar synthesis provides access to both **1** and **2** from the same intermediate (**8**) with complete control of regio and stereochemistry.

ACKNOWLEDGMENTS

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13. The sample of methyl α-D-kijanoside was kindly provided by Dr. A. K. Mallams of Schering-Plough Corp., Bloomfield, NJ.