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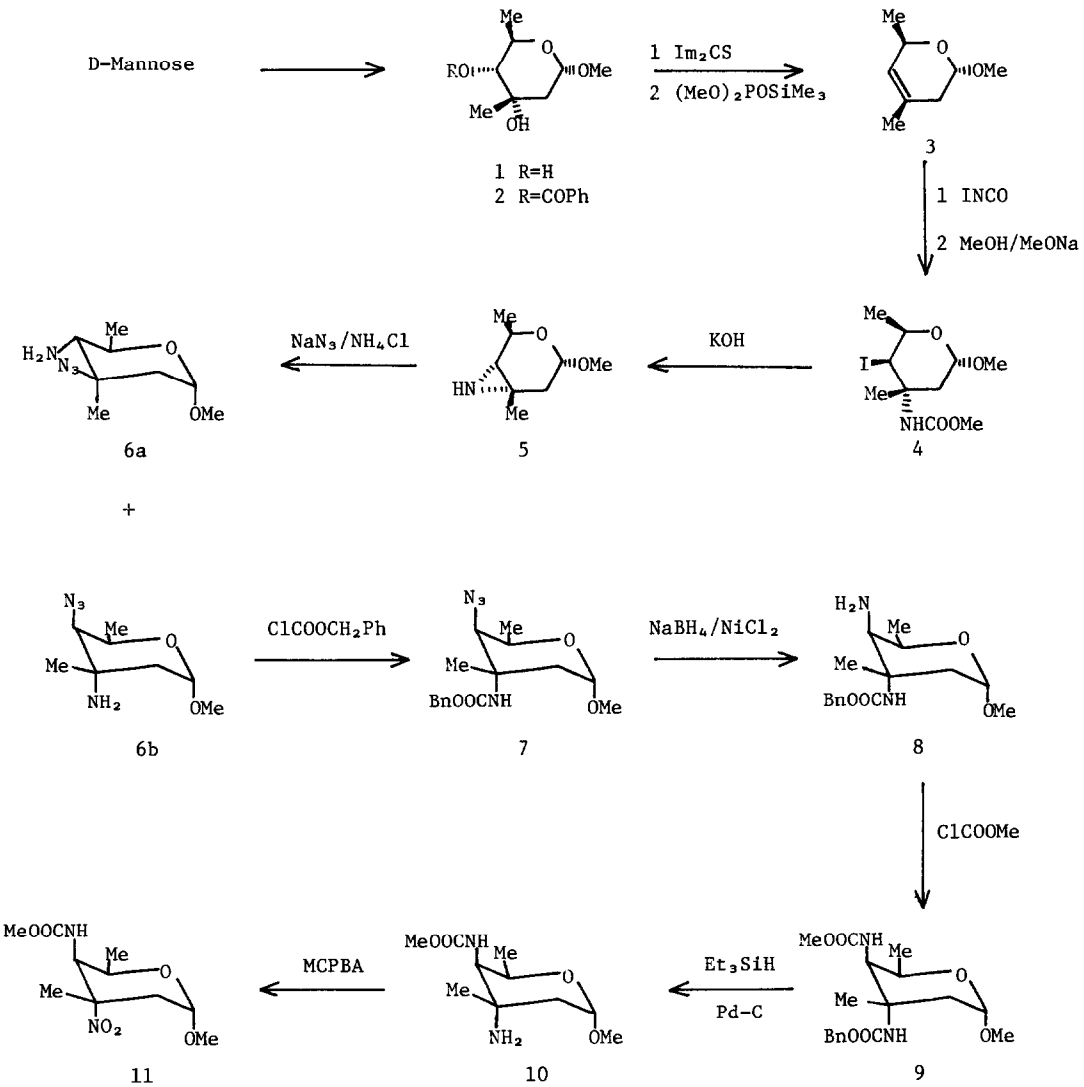
# SYNTHESIS AND ABSOLUTE CONFIGURATION OF METHYL α-TETRONITROSIDE (KIJANOSIDE)

Keishi Funaki, Kei Takeda, and Eiichi Yoshii*
*Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University*
*Sugitani 2630, Toyama 930-01, Japan*

*Abstract*: Synthesis of methyl α-D-tetronitroside(11) from D-mannose via methyl α-D-mycaroside(1) established the D-configuration for tetronitrose(=kijanose), a novel nitro sugar which occurs as a component of the antitumor antibiotics tetrocarcins A and B, and kijanimicin.

Tetronitrose(or kijanose) is an unusual methyl-branched nitro sugar recently discovered as one of the sugar components of antitumor antibiotics tetrocarcins A and B,[1] and kijanimicin[2] respectively. Although its structure was definitely determined by X-ray crystallography[1] to be 2,3,4,6-tetradeoxy-4-(methoxycarbonylamino)-3-*C*-methyl-3-nitro-*xylo*-hexopyranose and D-configuration was assigned by application of Hudson's rule of isorotation,[2] confirmation of the proposed absolute configuration by the synthesis has been a subject of our interest in this field. Herein we describe the synthesis of the methyl glycoside of this natural sugar from D-mannose via D-mycarose which led to conclusive proof of the proposed D-configuration.

Methyl α-D-mycaroside(1), mp 55.5-56.5°C, $[\alpha]_D$ +138°($CHCl_3$), prepared from D-mannose via 4-*O*-benzoyl-2,6-dideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside(2),[3] was reacted with N,N'-thiocarbonyldiimidazole by usual manner[4] and the resulting thiocarbonate was without purification heated in dimethyl trimethylsilyl phosphite[5] at 130-140°C for 4 hr. The unsaturated sugar 3 obtained by this two step sequence[6] and contaminated with a small amount of β-anomer could be readily isolated in 77% yield after hydrolytic removal of the excess phosphite and short path column chromatography of the crude product. The oily 3 was reacted with iodine isocyanate[7] at room temperature for 5 hr and the resulting addition product was directly treated with methanol in the presence of sodium methoxide to give iodo-carbamate(4) as a single isomer,[11] mp 76-76.5°C, $[\alpha]_D$ +140°($CHCl_3$). The compound 4 was then refluxed in aqueous methanol containing 2.3 equiv of KOH for 5 hr to afford the aziridine as an oil.[11] Nucleophilic ring opening of the aziridine 5 with sodium azide


D-Mannose
1 R=H
2 R=COPh
1 Im2CS
2 (MeO)2POSiMe3
3
1 INCO
2 MeOH/MeONa
4
KOH
5
NaN3/NH4Cl
6a
+
6b
ClCOOCH2Ph
7
NaBH4/NiCl2
8
ClCOOMe
9
Et3SiH
Pd-C
10
MCPBA
11

was performed in the presence of ammonium chloride in refluxing ethanol.[7] The regioisomers 6a(oil, $[\alpha]_D$ +197°($CHCl_3$)) and 6b(mp 37.5-38.5°C, $[\alpha]_D$ +186.5°($CHCl_3$)) formed in a ratio of ca. 2:3 and in a combined yield of 48% from 4 were readily separated by silica gel chromatography, and their structures were determined by $^1H$ NMR spectra by comparing the chemical shifts and coupling constants of 4-H: 6a, δ 2.55(d, $J$=10 Hz): 6b, δ 2.79(d, $J$=1 Hz).[11] The amino group of the desired isomer 6b was then protected by N-benzyloxycarbonylation to give 7,[11] the azide group of which was reduced with sodium borohydride and nickel chloride[8] at room temperature for 15 min. Methyl 2,3,4,6-tetradeoxy-4-amino-3-*C*-methyl-3-benzyloxycarbonylamino-D-*xylo*-hexopyranoside(8) obtained as an oil($[\alpha]_D$ +84.5°($CHCl_3$))[11] by this procedure was N-methoxycarbonylated by usual manner to give the dicarbamate 9($[\alpha]_D$+145°($CHCl_3$)),[11] which was subjected to hydrogenolysis using triethylsilane and palladium carbon[9] in methanol to give free 3-amino compound 10[11] in an overall yield of 55% from 6b. The final step leading to methyl α-D-tetronitroside from 10 was carried out by oxidation with m-chloroperbenzoic acid[10] in dichloromethane at room temperature for 20 min and the structure of the syrupy product isolated by silica gel chromatography in 58% yield was fully characterized by mass and nmr spectra.[11] Comparison of $[\alpha]_D$ +152°($CHCl_3$) of our synthetic methyl α-D-tetronitroside with the reported rotations, $[\alpha]_D$ +138°($CHCl_3$)[1] and $[\alpha]_D$ +130.0°(MeOH),[2] indicated clearly that the natural tetronitrose(or kijanose) belongs to D-series.

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11) 4, $^1$H NMR($CDCl_3$)δ: 1.20(d, J=6 Hz, 6-H), 1.63(br d, J=14 Hz, 2-$H_{eq}$), 1.69(s, 3-Me), 2.18(dd, J=14, 4 Hz, 2-$H_{ax}$), 3.33(qd, J=6, 0.5 Hz, 5-H), 3.38(s, 1-OMe), 3.62(s, COOMe), 4.65(br s, 4-H), 4.74(dd, J=4, 3 Hz, 1-H), 6.50(br s, NH).

5, $^1$H NMR($CDCl_3$)δ: 1.23(s, 3-Me), 1.39(d, J=6 Hz, 6-H), 1.76(br s, 4-H), 2.00(2H, diffused d, 2-H), 3.34(s, 1-OMe), 4.03(q, J=6 Hz, 5-H), 4.67(t, J=3 Hz, 1-H).

6a, $^1$H NMR($CDCl_3$)δ: 1.25(s, 3-$NH_2$), 1.29(d, J=6 Hz, 6-H), 1.47(s, 3-Me), ca. 2.0(2H, m, 2-H), 2.55(d, J=10 Hz, 4-H), 3.35(s, 1-OMe), 3.56(qd, J=10, 6 Hz, 5-H), 4.77(dd, J=4, 2 Hz, 1-H).

6b, $^1$H NMR($CDCl_3$)δ: 1.24(s, 3-Me), 1.35(d, J=6 Hz, 6-H), 1.57(dt, J=15, 1 Hz, 2-$H_{eq}$), 1.87 (dd, J=15, 4 Hz, 2-$H_{ax}$), 1.98(br s, 3-$NH_2$), 2.79(br s, 4-H), 3.38(s, 1-OMe), 4.35(qd, J=6, ≃1 Hz, 5-H), 4.78(d, J=4 Hz, 1-H); MS(EI)*m/e*(rel intensity): 201($M^+$+1, <0.1), 200($M^+$, 0), 169(4), 141(3), 101(55), 86(100).

7, $^1$H NMR($CDCl_3$)δ: 1.34(d, J=6 Hz, 6-H), 1.63(s, 3-Me), 1.58(dd, J=15, ≃1 Hz, 2-$H_{eq}$), 1.92 (dd, J=15, 4 Hz, 2-$H_{ax}$), 3.41(s, 1-OMe), 3.87(br s, 4-H), 4.25(qd, J=6, ≃1 Hz, 5-H), 4.78 (d, J=4 Hz, 1-H), 4.97 and 5.17(d, J=12 Hz, $COOCH_2$), 6.40(br s, 3-NH), 7.45(s, Ph); MS(EI) *m/e*(rel intensity):334($M^+$, 0), 303(1), 144(35), 100(100), 91(100).

8, $^1$H NMR($CDCl_3$)δ: 1.20(d, J=6 Hz, 6-H), 1.29(s, 4-$NH_2$), 1.52(s, 3-Me), 1.52(d, J=15 Hz, 2-$H_{eq}$), 1.88(dd, J=15, 4 Hz, 2-$H_{ax}$), 3.29(d, J≃1 Hz, 4-H), 3.39(s, 1-OMe), 4.26(qd, J=6, 1 Hz, 5-H), 4.72(d, J=4 Hz, 1-H), 5.03 and 5.16(d, J=13 Hz, $COOCH_2$), 6.37(br s, 3-NH), 7.43(s, Ph); MS(EI)*m/e*(rel intensity):309($M^+$, <0.1), 277(3), 276(2), 252(43), 236(71), 178(35), 157 (68), 56(100).

9, MS(EI)*m/e*(rel intensity): 366($M^+$, <0.1), 252(70), 234(12), 220(6), 190(12), 184(13), 176 (7), 156(14), 148(27), 115(100).

10, $^1$H NMR($CDCl_3$)δ: 1.10(s, 3-Me), 1.17(d, J=6 Hz, 6-H), 1.61(2H, br s, 2-H), 2.06(br s, 3-$NH_2$), 3.17(br d, J=10 Hz, 4-H), 3.37(s, 1-OMe), 4.42(q, J=6 Hz, 5-H), 4.74(diffused s, 1-H), 4.97(br d, J=10 Hz, 4-NH); MS(EI)*m/e*(rel intensity): 232($M^+$, <1), 201(2), 157(8), 118(100), 115(56), 100(80), 86(27).

11, $^1$H NMR($CDCl_3$)(200 MHz)δ: 1.19(d, J=6.4 Hz, 6-H), 1.54(s, 3-Me), 1.79(dd, J=15.5, 4.1 Hz, 2-$H_{ax}$), 2.77(d, J=15.5 Hz, 2-$H_{eq}$), 3.24(s, 1-OMe), 3.73(s, COOMe), 4.27(q, J=6.4 Hz, 5-H), 4.49(d, J=9.8 Hz, 4-H), 4.65(d, J=4.1 Hz, 1-H), 4.98(d, J=9.8 Hz, 4-NH); MS(EI)*m/e*(rel intensity): 262($M^+$, <1), 231(12), 184(14), 172(22), 156(13), 140(35), 128(100).

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