Tetrahedron Letters,Vol.30,No.17,pp 2263-2264,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

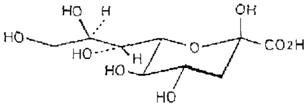
IMPROVED SYNTHESES OF TWO 3-DEOXYALD-2-ULOSONIC ACIDS(KDN,KDO) BY CONDENSATION OF OXALACETIC ACID WITH ALDOSES FOLLOWED BY Ni^{2+} CATALYZED DECARBOXYLATION[1)]

Ryuichi Shirai and Haruo Ogura*

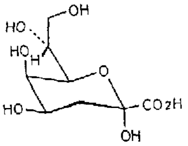
School of Pharmaceutical Sciences, Kitasato University,
Shirokane, Minato-ku, Tokyo 108, Japan

ABSTRACT : Condensation of oxalacetic acid with D-mannose and D-arabinose followed by Ni^{2+}catalyzed decarboxylation gave 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid(KDN) and 3-deoxy-D-*manno*-2-octulosonic acid(KDO) respectively in high chemical yield and high diastereoselectivity.

3-Deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid(KDN,**1**) was isolated from polysialoglycoprotein(PSGP) of rainbow trout eggs.[2)] Terminal capping of oligo(poly)sialylchains by the KDN residues protects these chains from exosialidases, thereby helping them to perform some required, but as yet unidentified function during egg activation or early development. 3-Deoxy-D-*manno*-2-octulosonic acid(KDO,**2**) is a characteristic sugar component of lipopolysaccharides(LPS) and capsular polysaccharides which occur in the cell surface of Gram negative bacteria and carry important biological actions.[3)]



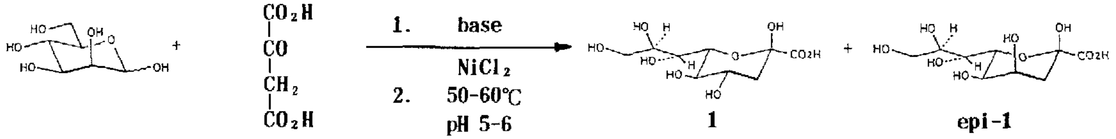
1



2

Syntheses of 3-deoxyald-2-ulosonic acids, especially **2** and its derivatives, have been reported by many groups.[1-8)] It is evident that the most concise synthetic method of **2** is condensation of oxalacetic acid with D-arabinose under aqueous basic condition followed by decarboxylation.[6,7)] However, the chemical yield of **2** by this reaction is low and is not reproducible because the decarboxylation condition has not so far been optimized. By the reported procedure,[3,7)] spontaneous decarboxylation of aldol aduct is very slow. Actually, Ungar reported that dicarboxylic aldol aduct was obtained by anion exchange chromatography.[3)] On the other hand, Redmond *et al.* reported that treatment of $2 \cdot NH_3$ with dilute acid gave 2,7-anhydro-3-deoxy-α-D-*manno*-2-octulofuranosonic acid because of its instability to acid.[9)] These results strongly indicate that decarboxylation of aldol aduct must be performed completely under mild conditions.

The polyvalent metal ion catalyzed decarboxylation of oxalacetic acid has been studied in detail and has served as a model system for the elucidation of an enzyme mechanism.[10)] We wish to report the improved syntheses of **1** and **2** by condensation of oxalacetic acid with aldoses followed by Ni^{2+}catalyzed decarboxylation of aldol aduct in one pot reaction. The reaction condition was optimized on the synthesis of **1**. Condensation was performed essentially by reported procedure(Table).[3,7)] Decarboxylation was performed in the presence of $NiCl_2$ (pH 5-6,60℃,1 hour). In the absence of $NiCl_2$, decarboxylation of aldol aduct required more drastic conditions (pH 5-6,80℃, 4 hours).



Run	Condensation condition	$NiCl_2$***	Yield (%)	1 : epi-1
1*	pH 10 (aq.NaOH)	10 mol%	11	4.3 : 1
2**	pH 10 (aq.NaOH-$NiCl_2$)	10 mol%	13	1 : 1
3*	pH 11 (aq.NaOH)	1 mol%	69	4.3 : 1
4*	pH 11 (aq.NaOH-Na_2CO_3)	1 mol%	70	4.2 : 1

* $NiCl_2$ was added to the reaction mixture in decarboxylation step

** $NiCl_2$ was added to the reaction mixture in condensation step

*** Relative amount to oxalacetic acid

In runs 1 and 2 (condensation pH 10), chemical yield was very low in each case. In run 1, diastereoselectivity was high to give the desired **1** predominantly. In run 2, on the other hand, diastereoselectivity was completely lost. Ratio of **1** / **epi-1** was determined by 300MHz ^{1}H-NMR spectra as an ammonium salt in D_2O. In runs 3 and 4 (condensation pH 11), **1** was obtained in high chemical yield and high diastereoselectivity.

By the same procedure as run 3, **2** was synthesized from D-arabinose in 66% chemical yield as known ammonium salt(**2**・NH_3). The diastereoselectivity of this reaction at C-4 chiral center was determined to be very high(>10:1) by 300MHz ^{1}H-NMR spectrum in D_2O. 2,7-anhydro-deriavtive of **2** was not formed by this decarboxylation condition.[9]

In conclusion, **1** and **2** were synthesized practically in high chemical yield and in high diastereoselectivity by improved condensation-decarboxylation procedure.

Acknowledgements: This work was supported in part by Grants-in-Aid for Scientific Research (No. 62771852, No. 63470129) from the Ministry of Education, Science and Culture, and by Research Aid of Inoue Foundation for Science.

References: 1)Part XX of series "Studies on Sialic Acid". 2)D.Nadano,M.Iwasaki,S.Endo,K. Kitajima,S.Inoue,Y.Inoue,*J.Biol.Chem.*,**261**,11550(1986). 3)F.M.Ungar, *Adv.Carbohydr.Chem. Biochem.*,**38**,323(1981). 4)R.Shirai,M.Nakamura,S.Hara,H.Takayanagi,H.Ogura,*Tetrahedron Lett.*,**29**,4449(1988). 5)R.Ramage,G.W.Rose,A.M.MacLead,*ibid.*,**29**,4877(1988) and references cited therein. See also ref. 6-8. 6)J.W.Cornforth,M.E.Firth,A.Gottshark,*Biochem.J.*,**68**,57 (1958); P.M.Carroll,J.W.Cornforth, *Biochim.Biophys.Acta*,**39**,161(1960). 7)M.A.Ghalambor,E. M.Levine,E.C.Heath,*J.Biol.Chem.*,**241**,3207(1966); C.Hershberger,M.Davis,S.B.Binkley,*ibid.*, **243**,1585(1968); P.A.McNicholas,M.Batley,J.W.Redmond,*Carbohydr.Res.*,**146**,219(1986). 8)D. Charon,S.Szabó,*J.Chem.Soc.*,*Perkin I*,1971(1980) and references cited therein. 9)P.A. McNicholas,M.Batley,J.W.Redmond,*Carbohydr.Res.*,**165**,17(1987). 10)H.A.Krebs,*Biochem.J.*,**36**, 303(1942); J.F.Speck,*J.Biol.Chem.*,**178**,315(1949); R.Steinberger,F.H.Westheimer,*J.Am.Chem. Soc.*,**73**,429(1951); F.H.Westheimer,in *The Enzymes*,(P.D.Boyer,ed)2nd Ed.,Vol.1,pp.270-278 (1959); E.Gelles,R.W.Hay,*J.Chem.Soc.*,3673(1958); E.Gelles,Salama,*ibid.*,3683(1958); *idem, ibid.*,3689(1958); K.M.Herrmann,M.D.Poling,*J.Biol.Chem.*,**250**,6817(1975).

(Received in Japan 9 March 1989)