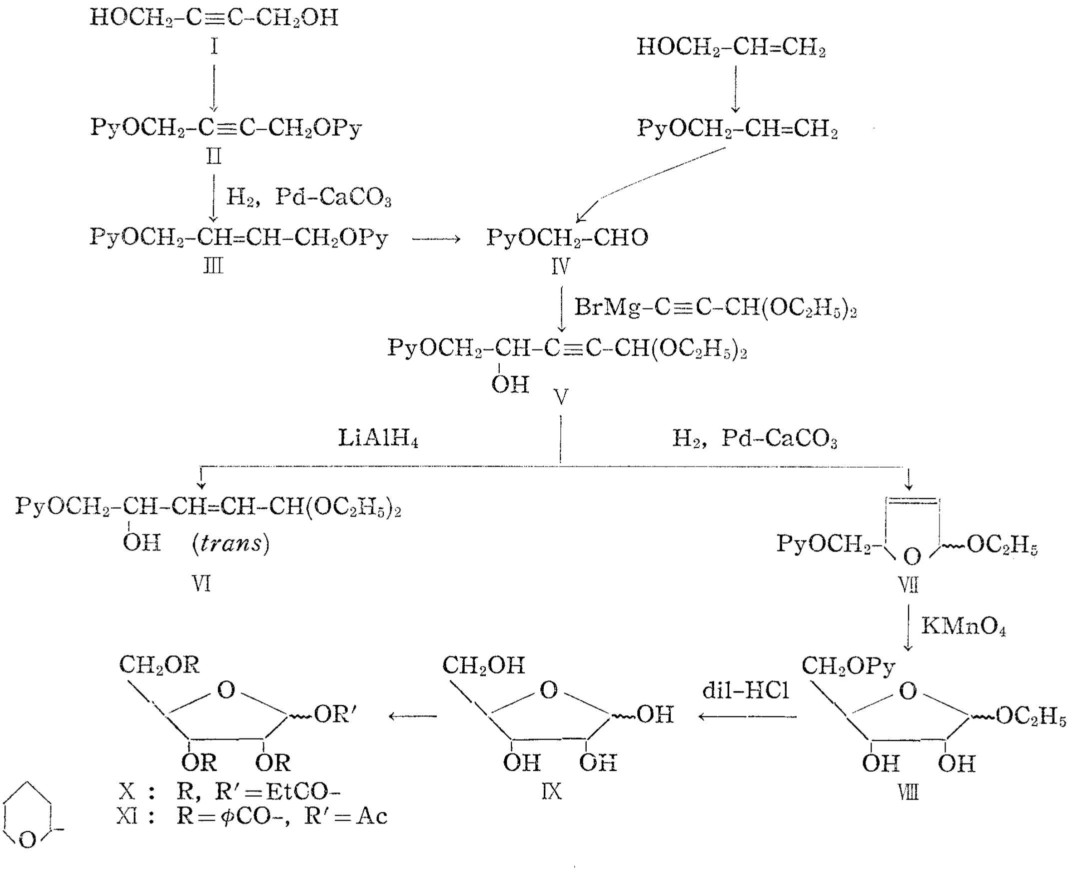
UDC 547.314.07:547.456.07

33. **Issei Iwai, Tadahiro Iwashige, Motoji Asai, Kazuo Tomita, Tetsuo Hiraoka, and Junya Ide**: Studies on Acetylenic Compounds. XXIX. A New Method for Synthesis of DL-Ribose.*[1],[2]

(*Takamine Research Laboratory, Sankyo Co., Ltd.**[3])

In the previous papers Iwai, Iwashige, *et al.*[1~3] reported the total synthesis of four kinds of pentoses from acetylenic compounds. There seemed to exist two essential problems in synthesizing a sugar: (1) How to hydrogenate a triple bond partially to a double bond. (2) How to hydroxylate the double bond to a diol. Keeping these points in mind, we chose to study in more detail the steric course of the reduction of acetylenic compounds and subsequent hydroxylation of the resulted double bond to a diol. Thus DL-arabinose was synthesized from 5-ethoxy-4-penten-2-yn-1-ol via 5-ethoxy-2,4-pentadien-1-ol, no other isomeric pentoses were formed.[3]

This paper describes a new synthetic method of DL-ribose from an acetylenic compound by which no other pentoses were produced.



---

*[1] Part XXVIII: I. Iwai, K. Tomita. This Bulletin, **11**, (1963).

*[2] Presented before the 5th Annual Meeting of Kantō section of Pharmaceutical Society of Japan, Nov. 11, 1961.

*[3] Nishi-shinagawa, Shinagawa-ku, Tokyo (岩井一成, 岩重忠博, 浅井素次, 富田和男, 平岡哲夫, 井手純也).

1) I. Iwai, T. Iwashige: This Bulletin, **9**, 316 (1961).

2) T. Iwashige: *Ibid.*, **9**, 492 (1961).

3) I. Iwai, K. Tomita: *Ibid.*, **9**, 976 (1961).

1,4-Bis(tetrahydro-2-pyranyloxy)-2-butyne (II) prepared from butynediol (I) and dihydropyran was catalytically hydrogenated to the corresponding dien-diether III which was ozonolized to give (terahydro-2-pranyloxy)-acetaldehyde (IV). IV was also obtained from the tetrahydropyranyl ether of allyl alcohol by ozonolysis. IV, when reacted with propargyl acetal magnesium bromide, gave 1,1-diethoxy-5-(tetrahydro-2-pranyloxy)-2-pentyn-4-ol (V) ($b.p_{0.1}$ 141～144°). Partial reduction of V led to give different kinds of products dependent upon reducing agents used. Lithium aluminum hydride[2,4] reduction of V gave DL-*trans*-1,1-diethoxy-5-(tetrahydro-2-pyranyloxy)-2-penten-4-ol (VI), $b.p_{0.06}$ 130～135° (bath temp.) which showed absorptions at 3600 cm^{-1} (-OH) and 1660 cm^{-1} (-C=C-) in the infrared spectrum. On the other hand, 2-ethoxy-5-(tetrahydro-2-pyranyloxy)-methyl-2,5-dihydrofuran (VII) was obtained as a main product by catalytic hydrogenation of V using a Lindlar catalyst. VII did not exhibit any infrared absorption due to OH but a characteristic band at 1620 cm^{-1}, which is similar to the double bond absorption of cyclopenten. Heilbron,[5] *et al.* reported that catalytic hydrogen ation of1,1-diethoxy-4-methyl-2-hexyn-4-ol afforded the cyclic compound of 2-ethoxy-5-ethyl-5-methyl-2,5-dihydrofuran. Also in partial reduction of a triple bond in V, cyclization seemed to have occurred to give a dihydrofuran derivative. Hydroxylation of VII with potassium permanganate provided a viscous oily product of $b.p_{0.0005}$ 145～155° (bath temp.) which was analyzed for 2-ethoxy-5-(tetrahydro-2-pyranyloxy)methyltetrahydro-3,4-furandiol (VIII). The infrared spectrm of VIII showed an absorption at 3450 cm^{-1} due to OH, but the bands at 1620 cm^{-1} (-C=C-) and 730 cm^{-1} $\underset{cis}{(\text{-}\overset{\overset{H}{|}}{C}=\overset{\overset{H}{|}}{C}\text{-})}$ which were found in III, disappeared. Acylation of the syrupy product obtatned from VIII by treatment with dil. hydrochloric acid, afforded a viscous oil which was analyzed for pentose tetrapropionate (X).[1,6] Results of gas chromatography[7] of X using D-ribose tetrapropionate as a reference are shown in Fig. 1.

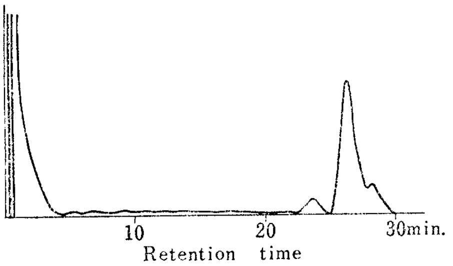


Fig. 1.

Column : 6 mm × 6 ft, 1% SE-30 on 60～80 mesh Chromosorb-W
Column Temp. : 152°
Cell Temp. : 160°
Flashing Temp. : 265°
Argon Press. : 2 kg./cm^2
Detector : Argon Ionization Detector

As shown in Fig. 1, the main peak of product X appeared at a retention time of 26.4 minutes, which was also the case with D-ribosetetrapropionate. The shoulder following the main peak, was also observed in D-ribosetetrapropionate, and this is probably due to the presence of a small amount of a pyranose form. Besides these peaks, X showed a minor one at a retention time of 23.4 minutes which was also observed in the case of the tetrapropionates of D-lyxose, D-xylose, and D-arabinose. It is not certain whether this peak depended on DL-lyxose tetrapropionate which would be expected to form by our method. The estimation of retention analysis was proportional to 93:7. From these results, it is concluded that DL-ribose was stereospecifically produced. The colorless oily product prepared from VIII by treatment with dil. hydrochloric acid followed by

---

4) J. Attenburrow, A.F.B. Cameron, *et al.* : J. Chem. Soc., **1952**, 1094; R. Ahmad, F. Sondheimer : *Ibid.*, **1952**, 4089.
5) I.M. Heilbron, E.R.H. Jones, H.P. Koch : J. Chem. Soc., **1942**, 735.
6) C.D. Hurd, K.M. Gordon : J. Am. Chem. Soc., **63**, 2657 (1941).
7) W.J.A. Vanden Heuvel, E.C. Horning : Biochem. & Biophys. Res. Commun., **4**. 399 (1961); N, Ikekawa : Kagaku no Ryōiki, **15**, 449 (1961).

ion exchange resin chromatography on Dowex-I,[2,8] showed only one spot Rf=0.32 on a paper chromatogram and gave a phenylosazone, m.p. 166~168° and 1-O-acetyl-2,3,5-tri-O-benzoyl-β-DL-ribofranose (XI), m.p. 115~117°. The infrared spectrum of XI in carbon tetrachloride solution was in good agreement coincided with that of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose[9] as shown in Fig. 2.

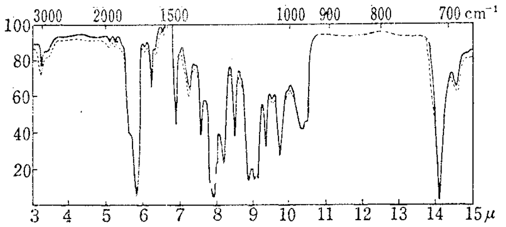


Fig. 2. Infrared Absorption Spectra (in CCl_4)

—— 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-DL-ribofuranose
------ 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose

Nielsen, Elming and Clauson-Kaas[10] reported that hydroxylation of *cis*-2,5-dimethoxy-2,5-dihydrofuran with potassium permanganate afforded only one *cis* diol, inspite of the fact that two *cis*-isomers were theoretically expected. In the case of VII, two isomers are also conceivable namely, one is $PyOCH_2/OC_2H_5$ *cis*, and the other is *trans*. Even if VII was a mixture of the two isomers, *cis*-hydroxylation would take place in the opposite side of a more bulky group to give DL-ribose stereospecifically. Actually we obtained exclusively DL-ribose by this hydroxylation.

Experimental

1,4-Bis(tetrahydro-2-pyranyloxy)-2-butyne (II)——To 30 g. of butyndiol were added 118.3 g. of dihydropyran and 3 drops of conc. HCl. When the mixture was stirred, evolution of heat took place and the temperature rose to 70°. After the evolution of heat had subsided, it was warmed to 80° and stirred for 2 hr. Upon cooling, the reaction mixture was washed with a conc. aq. Na_2CO_3, dried over anhyd. K_2CO_3 and distilled *in vacuo* to yield 76.1 g. of 1,4-bis(tetrahydro-2-pyranyloxy)-2-butyne, b.p$_3$ 150°. *Anal.* Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.82; H, 8.66.

1,4-Bis(tetrahydro-2-pyranyloxy)-2-butene (III)——A solution of 10 g. (0.0393*M*) of 1,4-bis(tetrahydro-2-pyranyloxy)-2-butyne (II) in 60 cc. of AcOEt was hydrogenated at atmospheric pressure in the presence of 1.8 g. of Lindlar catalyst. After 1030 cc. of H_2 was absorbed at 23°, the solution was filtered to remove the catalyst and the filtrate was evaporated. The residue was distilled *in vacuo* to yield 7.6 g. of 1,4-bis(tetrahydro-2-pyranyloxy)-2-butene, b.p$_{0.08}$ 104~106°. *Anal.* Calcd. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.52; H, 9.31.

Allyl tetrahydro-2-pyranyl Ether[11]——To 468 g. of freshly distilled dihydropyran was added 0.5 cc. of conc. HCl. Then, 323 g. of allyl alcohol was added dropwise. The evolution of heat was observed during the addition and the temperature was maintained below 60° with occasional cooling. After all of allyl alcohol was added, the reaction mixture was stirred at room temperature for a further 2 hr., washed with a small amount of a conc. aq. Na_2CO_3, and dried over anhyd. K_2CO_3. Distillation under reduced pressure gave 506 g. of allyl tetrahydro-2-pyranyl ether, b.p$_{15}$ 61~62°.

(Tetrahydro-2-pyranyloxy)acetaldehyde (IV)——a) From allyl tetrahydro-2-pyranyl ether: To 2 L. of purified anhyd. CH_2Cl_2, was added 100 g. (0.7*M*) of allyl tetrahydro-2-pyranyl ether and the solution ozonized (velocity: 250 L./hr., voltage: 65 v) under cooling at −50°~−60°. Ozonisation was stopped after 25% excess of the calculated amount of O_3 was passed through. Then, the reaction mixture was allowed to warm to room temperature and transferred to a 5 L. three necked round flask. Then, 100 g. of Zn dust and 100 cc. of AcOH containing 15 cc. of H_2O were added in small portions to decompose the ozonide over a period of an hour, the temperature being maintained below 30° with occasional cooling. The resulting mixture was stirred at room temperature for a further 2 hr. and the solid material was filtered off, and washed with about 300 cc. of CH_2Cl_2. The combined CH_2Cl_2 solution was washed twice with $NaHCO_3$ solution, three times with sat. aq. NaCl, deied over Na_2SO_4, and

---

8) J.X. Khym, L.P. Zill: J. Am. Chem. Soc., **74**, 2090 (1952); K. Mori, M. Nakamura: Nippon Nōgei Kagaku Kaishi, **34**, A5 (1960).
9) H.M. Kissman, C. Pidacks, B.R. Baker: J. Am. Chem. Soc., **77**, 21 (1955).
10) J.T. Nielsen, N. Elming, N. Clauson-Kaas: Acta. Chem. Scand., **12**, 63~67 (1958).
11) G.F. Woods, D.N. Kramer: J. Am. Chem. Soc., **69**, 2246 (1947).

evaporated. The residue was distilled *in vacuo* to yield 67 g. of tetrahydro-2-pyranyloxyacetaldehyde, b.p$_9$ 74～76°. *Anal.* Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found : C, 58.25; H, 8.49.
b) From 1,4-bis(tetrahydro-2-pyranyloxy)-2-butene (III) : HCHO[12] gas generated from 75 g. of paraformaldehyde was introduced to 1.3 L. CH_2Cl_2 under ice-water cooling. Then, to this solution was added 128 g. (0.5*M*) of 1,4-bis(tetrahydro-2-pyranyloxy)-2-butene (III) and the solution ozonized over a period of 4.5 hr. at −50° (O_3 concentration : 6.098 g./hr.). After ozonisation, 130 g. of Zn dust was added to the reaction mixture, and then 75 cc. of AcOH containing 3.75 cc. H_2O was added dropwise over a perioed of 3 hr. at such a rate that the inner temperature was maintained between 15° and 19° with ice-water cooling. After the addition, the resulting mixture was stirred at room temperature for 30 min. The solid material was filtered off, and washed with about 400 cc. CH_2Cl_2. The combined CH_2Cl_2 solution was washed with an aq. $NaHCO_3$ and than a sat. aq. NaCl until neutral to lithmus paper, dried over anhyd. Na_2SO_4 and evaporated. Distillation of the residue gave 91.5 g. of b.p$_{10}$ 75～80°. This was identified as (tetrahydro-2-pyranyloxy)acetaldehyde, obtained method a), by the comparison of both IR spectra.

DL-1,1-Diethoxy-5-(tetrahydro-2-pyranyloxy)-2-penten-4-ol (V)——To the Grignard solution prepared from 25.8 g. of Mg and 115.8 g. of EtBr in 500 cc. of anhyd. tetrahydrofuran was added dropwise 123 g. of propargyldiethylacetal in 500 cc. of tetrahydrofuran, cooled at 3°～5° and the mixture stirred at room temperature for 3 hr. To the above reaction mixture was added dropwise under cooling at 0°～3° 126.4 g. of (tetrahydro-2-pyranyloxy)acetaldehyde (IV) in 500 cc. of tetrahydrofuran over a period of 3 hr. and the mixture stirred at room temperature for 4 hr. and left overnight. A cold sat. aq. NH_4Cl was added slowly under cooling with ice-water to decompose the reaction product, and the aqueous layer was extracted with Et_2O (200 cc × 3.). The combined organic layers were washed with a sat. aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated. Distillation of the residue gave 90 g. of DL-1,1-diethoxy-5-(tetrahydro-2-pyranyloxy)-2-pentyn-4-ol (V), b.p$_{0.1}$ 141～144°, $n_D^{23.5}$ 1.4677. *Anal.* Calcd. for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found : C, 61.52; H, 8.88. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3550 (OH), 2230 (-C≡C-), 1000～1150 (-C-O-C-).

DL-*trans*-1,1-Diethoxy-5-tetrahydro-2-pyranyloxy)-2-penten-4-ol (VI)——To 0.95 g. (0.025*M*) of $LiAlH_4$ in 200 cc. of anhyd. Et_2O was added slowly 3 g. (0.011*M*) of DL-1,1-diethoxy-5-(tetrahydro-2-pyranyloxy)-2-pentyn-4-ol (V) in 50 cc. of anhyd. Et_2O, with stirring and ice-water cooling. The mixture was refluxed under stirring for 4 hr. and left overnight. After AcOEt was added to decompose the excess $LiAlH_4$, the Li-Al complex of the reaction product was decomposed with a cold sat. aq. NH_4Cl and the resulting aqueous layer was extracted three times with Et_2O. The combined Et_2O solutions were washed with a cold sat. aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated. The residue was distilled *in vacuo* to yield 2.0 g. of DL-*trans*-1,1-diethoxy-5(tetrahydro-2-pyranyloxy)-2-penten-4-ol (VI), b.p$_{0.06}$ 130～135° (bath temp.), n_D^{22} 1.4661, d^{16} 1.057. *Anal.* Calcd. for $C_{14}H_{26}O_5$: C, 61.26; H, 9.55. Found : C, 61.11; H, 9.30. M$_D$. Calcd. : 72.29. Found : 71.82. IR $\nu_{max}^{CCl_4}$ cm^{-1} : 3600 (OH), 1660 (-C=C-), 1000～1150 (-C-O-C-).

2-Ethoxy-5-(tetrahydro-2-pyranyloxy)methyl-2,5-dihydrofuran (VII)——A solution of 90 g. of DL-1,1-diethoxy-5-(tetrahydro-2-pyranyloxy)-2-pentyn-4-ol (V) in 180 cc. of AcOEt was hydrogenated in the presence of 10 g. of the Lindlar catalyst at atmospheric pressure, and 6150 cc. of H_2 was absorbed at 21°. The solution was filtered to remove the catalyst and the filtrate was evaporated. The residue was distilled *in vacuo* and divided into the following fractions.

fraction No.	b.p. at 0.2 mm. Hg. (°C)	Yield (g.)
1	～84	4.1
2	84～107	41.5
3	138～157	9.5

The second fraction was redistilled to yield 22 g. of 2-ethoxy-5-(tetrahydro-2-pyranyloxy)methyl-2,5-dihydrofuran (VII), b.p$_{0.15}$ 92～93°, n_D^{17} 1.4679, d^{17} 1.0841. *Anal.* Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found : C, 63.46; H, 8.50. M$_D$. Calcd. : 59.33. Found : 58.59. IR $\nu_{max}^{liq.}$ cm^{-1} : 1620 (-C=C-), 1000～1150 (-C-O-C-), 730 $\underset{(cis)}{\text{(-CH=CH-)}}$.

2-Ethoxy-5-(tetrahydro-2-pyranyloxy)methyltetrahydro-3,4-furandiol (VIII)——2-Ethoxy-5-(tetrahydro-2-pyranydro-2-pyranyloxy) methyl-2,5-dihydrofuran (VII) (20.5 g.) was dissolved in 110 cc. of Me_2CO containing 40 cc. of H_2O. To the above solution was added in small portions 10.8 g. of $KMnO_4$ under stirring and cooling at −15°～−20° over a period of 2 hr. After the addition, stirring was continued at room temperature for 30 min. and the mixture centrifuged to remove the colloidal MnO_2. The filtered MnO_2 was washed with CH_2Cl_2 and the aq. Me_2CO was also extracted with CH_2Cl_2. The

---

[12] cf. R. Criege, G. Blust, H. Zinke : Ber., **87**, 766 (1954); K. Tanabe, R. Hayashi, R. Takasaki : This Billetin, **9**, 1 (1961).

combined organic solutions were dried over anhyd. Na_2SO_4 and evaporated. The residue was distilled *in vacuo* to yield 7.6 g. of a viscous oil, b.p$_{0.0005}$ 145~155°, showing a positive HIO_4-$AgNO_3$ test. *Anal.* Calcd. for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found : C, 54.96; H, 8.01. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1} : 3450(OH), 1000~1200(-C-O-C-).

DL-Ribose (IX)——2-Ethoxy-5-(tetrahydro-2-pyranyloxy)methyltetrahydro-3,4-furandiol (VIII) (7.5 g.) was added to 50 cc. of 5% HCl and the mixture left at room temperature for 3 days. The reaction mixture was deacidified with Amberlite IR-4B and concentrated at room temperature under reduced pressure. The syrupy residue was dissolved in abs. EtOH, purified by adding benzene and decantation, and dried to give 3.5 g. of a syrup. A part of the syrup was acylated with propionic anhydride and pyridine to give a tetrapropionate, b.p$_{0.0003}$ 155~165°(bath temp.), which was subjected to the gas chromatography as described before. *Anal.* (tetrapropionate) Calcd. for $C_{17}H_{26}O_9$: C, 54.60; H, 6.95. Found : C, 54.71; H, 7.03.

The crude residue (3.2 g.) obtained above was purified through Dowex-1 ion exchange resin chromatography using 0.025*M* $K_2B_4O_7$ as an eluting agent to give 2.8 g. of a syrup. This syrup gave the following Rf value and derivatives.

Phenylosazone : m.p. 166~168°. *Anal.* Calcd. for $C_{17}H_{20}O_3N_4$: C, 62.18; H, 6.14; N, 17.06. Found : C, 61.31; H, 6.13; N, 16.91.

1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-DL-ribofuranose : m.p. 115~117°. *Anal.* Calcd. for $C_{28}H_{24}O_9$: C, 66.66; H, 4.80. Found : C, 66.15; H, 4.70.

Rf=0.32 (control D-ribose, Rf=0.32). Solvent : BuOH-H_2O-AcOH(4:5:1). Temp. : 20±1°. Time : 15.5 hr. Detection agent : Partridge reagent.

The authors express their deep gratitude to Prof. K. Tsuda, university of Tokyo, and to Dr. M. Matsui, Director of this laboratory for their kind guidance and encouragement throughout the course of this investigation. They are also greatly indebted to Dr. N. Ikekawa, the Institute of Physical and Chemicel Research, for his kind suggestions. The measurement of infrared and ultraviolet spectra was carried out by Messrs. H. Higuchi, and N. Higosaki and Miss N. Sawamoto, and microanalyses were performed by Dr. T. Onoe and Mr. H. Nagashima and Misses H. Ohtsuka and N. Gonda.

Summary

DL-Ribose was synthesized stereospecifically by oxidative hydroxylation of 2-ethoxy-5-(tetrahydro-2-pyranyloxy)methyl-2,5-dihydrofuran (VII), which was obtained by hydrogenation of DL-1,1-diethoxy-5-(tetrahydro-2-pyranyloxy)-2-pentyn-4-ol. DL-1,1-diethoxy-5-(tetrahydro-2-pyranyloxy)-2-pentyn-4-ol was prepared by the Grignard reaction of (tetrahydro-2-pyranyloxy)acetaldehyde with propargyl diethyl acetal magnesium bromide.

(Received March 6, 1962)