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Total Syntheses of Carbohydrates. IV. 2-Deoxy-DL-, L- and D-*erythro*-pentoses and Related Sugars

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5-Bromo-2,5-dideoxy-*threo*-pentono-γ-lactone (III) could be obtained stereoselectively from 3-hydroxy-4-pentenoic acid (I) by the reaction with *N*-bromosuccinimide in water. On successive treatment with an aqueous potassium hydroxide and an acid type cation exchange resin, bromolactone (III) gave stereoselectively 2-deoxy-*erythro*-pentono-γ-lactone (IV). Reduction of IV by means of bis(1,2-dimethylpropyl)borane afforded 2-deoxy-*erythro*-pentose (V). 3-Hydroxy-4-pentenoic acid (I) could be optically resolved. The (+)-acid yielded 2-deoxy-D-*erythro*-pentose (D-V) and the (−)-acid could be converted to 2-deoxy-L-*erythro*-pentose (L-V). 2,5-Dideoxy-*threo*-pentose (VIII) and 5-bromo-2,5-dideoxy-*threo*-pentose (IX) were obtained from bromo-lactone (III). Diethyl mercaptal of IX gave azido-compound (XI) in a low yield by the reaction with sodium azide. The conformation of γ-lactones (III, IV, and VII) and the mechanistic aspects of stereoselective reactions are discussed.

In the previous paper we reported the total synthesis of *rac*-2-deoxy-*erythro*-pentose.[1] The present paper deals with the syntheses of optically active forms of the carbohydrate. In spite of remarkable development of the total syntheses of carbohydrates, only two reports on total syntheses of optically active carbohydrates have been published. Fischer has reported the total syntheses of D- and L-mannoses, D- and L-glucoses and D-fructose starting from mannonic acid which had been derived from acrolein dibromide *via* DL-glucosazone.[2] After about 80 years, L-(−)-mycalose which is a constituent of various macrolide antibiotics was synthesized by Lemal, Pacht, and Woodward.[3] After the publication of preliminary report of the present paper,[4] the total synthesis of optically active kasuga-

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1) K. Mimaki, M. Masunari, G. Nakaminami, and M. Nakagawa, This Bulletin, **45**, 2620 (1972).

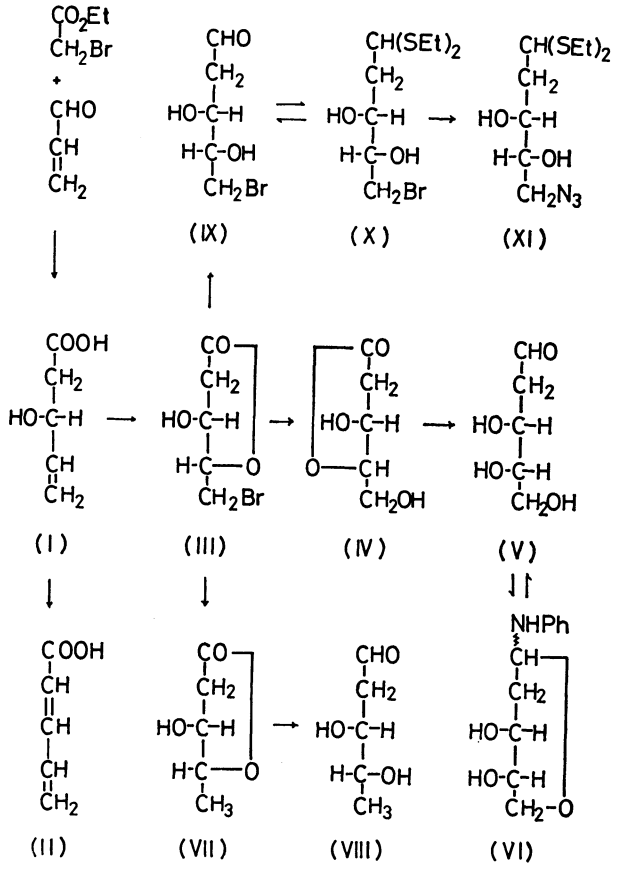
2) For summary, see, E. Fischer, *Ber.*, **23**, 2114 (1890).

3) D. M. Lemal, P. D. Pacht, and R. B. Woodward, *Tetrahedron*, **18**, 1275 (1962).

4) G. Nakaminami, M. Nakagawa, S. Shioi, Y. Sugiyama, S. Isemura, and M. Shibuya, *Tetrahedron Lett.*, **1967**, 3983.

mycin has been briefly reported by two groups.[5]

The following scheme illustrates the reaction sequence of total synthesis of 2-deoxy-L-*erythro*-pentose, however, the same scheme will be used in the description of syntheses of DL- and D-forms of the carbohydrate.



Scheme 1. Syntheses of 2-deoxy-L-*erythro*-pentose (L-V) and related sugars.

The Reformatsky reaction of acrolein with ethyl bromoacetate followed by alkaline hydrolysis afforded DL-β-hydroxy acid (I). Owing to ready dehydration to form pentadienoic acid (II), β-hydroxy acid (I) should be handled with care. Treatment of DL-β-hydroxy acid (I) with 0.5 equivalent of quinine followed by decomposition of the salt afforded (−)-β-hydroxy acid [(−)-I] which gave ultimately 2-deoxy-L-*erythro*-pentose (L-V). The hydroxy acid (I) obtained from the mother liquor of the quinine salt was resolved by means of quinidine salt to give (+)-β-hydroxy acid [(+)-I] which could be converted to 2-deoxy-D-*erythro*-pentose (D-V). The subsequent reactions were carried out with DL-compounds in the first place and then with optically active forms. It has been well-known that a terminal mono-substituted double bond is resistant to peracid oxidation.[6] Therefore, hydroxylation by means of potassium permanganate[7] was first attempted. The acetyl derivative of β-hydroxy acid (I) was treated with an aqueous solution of potassium permanganate under a neutral condition. In spite of the consumption of permanganate, no identifiable product could be isolated from the reaction mixture. Consequently, indirect hydroxylation *via* halohydrin[8] was applied to the hydroxy acid (I). Treatment of β-hydroxy acid (I) with *N*-bromosuccinimide in water followed by a chromatographic purification on silica gel[9] yielded syrupy bromolactone (III) in a yield of 57%. The (−)-acid [(−)-I] gave (+)-III and the (+)-acid [(+)-I] resulted in (−)-III. The by-products were found to be a complex mixture of highly polar compounds and could not be purified. Bromolactone (III) thus obtained was found to be homogeneous without contamination with *erythro*-isomer on the basis of tlc and NMR spectroscopy. The tlc and NMR spectra of IV and VII which were derived from III (see, below) indicate that these lactones are free from their epimers. This fact also supports the homogenity of bromolactone (III). The analytical data of III and its phenylhydrazide, and the IR (C=O, 1795 cm^{-1} in $CHCl_3$: γ-lactone) and NMR spectral data (see, following part) of III are consistent with the assigned structure. The fact that an aqueous solution of optically active III showed practically no change of rotation over a period of 2 weeks affords an additional evidence for γ-lactone structure of III. The immediate change of rotation of (+)-bromolactone (III, $[\alpha]_D$ +51°, H_2O) to $[\alpha]_D$ −3.4° on addition of a drop of concentrated aqueous sodium hydroxide indicates that the configuration of $C_{(4)}$ should belong to D-series according to the Hudson's lactone rule.[10] Consequently, the *O*-function at $C_{(4)}$ should be written in the right side in Fischer's projection formula. As is stated below, because the configuration of $C_{(3)}$ in bromolactone (III) is undoubtedly retained during the course of derivation to 2-deoxy-L-*erythro*-pentose (V), the hydroxyl group at $C_{(3)}$ in (+)-bromolactone (III) which gave the L-form of V, should be written in the left side in Fischer's projection formula indicating that bromolactone (III) has *threo*-configuration. Further evidence for *threo*-configuration of III was obtained by the preparation of 2,5-dideoxy-pentono-lactone (VII). Reduction by means of tri-*n*-butyltin hydride,[11] which had not yet been used in the field of carbohydrate chemistry,[12] was successfully adopted for the conversion of bromolactone (III) to dideoxy-pentono-lactone (VII)

5) Y. Suhara, F. Sasaki, K. Maeda, H. Umezawa, and M. Ohno, *J. Amer. Chem. Soc.*, **90**, 6559 (1968); S. Yasuda, T. Ogasawara, S. Kawabata, I. Iwataki, and T. Masumoto, *Tetrahedron Lett.*, **1969**, 3969.

6) J. Böseken and J. S. P. Blumberger, *Rec. Trav. Chim. Pays-Bas*, **44**, 90 (1925); H. Meerwein, *J. Prak. Chem.*, **113**, 9 (1926); T.W. Findley, D. Swern, and J. T. Scanlan, *J. Amer. Chem. Soc.*, **67**, 412 (1945); D. Swern, G. N. Billen, and J. T. Scanlan, *ibid.*, **68**, 1504 (1946).

7) E. J. Witzemann, W. L. Evans, H. Hass, and E. F. Schroeder, "Organic Syntheses," Coll. Vol. II, p. 307 (1958).

8) R. A. Raphael, *J. Chem. Soc.*, **1949**, S 44.

9) Chromatography on silica gel was found to be superior to that on neutral alumina reported in the preliminary report.[4]

10) J. Stanĕk, M. Černy, J. Kocourek, and J. Pacák, translated by K. Mayer, "The Monosaccharides," Academic Press, New York and London, (1963), p. 55.

11) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, London, and Sydney, (1967), p. 1192.

12) Cf., for example, S. Hanessian, *Advan. Carbohyd. Chem.*, **21**, 143 (1966); J. E. G. Barnett, *ibid.*, **22**, 177 (1967).

instead of the usual hydrogenolysis.[13] The isolation of dideoxy-lactone (VII) from the reaction mixture could be performed easily owing to the high solubility of VII in water. The spectroscopic data of 2,5-dideoxy-pentono-lactone (VII) were found to be consistent with the structure of VII [IR: 1783 cm^{-1} (γ-lactone); NMR: δ 1.25 (doublet, methyl H)]. Dideoxy-lactone obtained from (+)-bromolactone [(+)-III] showed dextrorotation in an aqueous solution and no change of rotation could be observed over 2 weeks supporting γ-lactone structure. The specific rotation of (+)-dideoxy-lactone [(+)-VII, $[\alpha]_D$ +58°] immediately changed to +13° on addition of a drop of concentrated aqueous solution of sodium hydroxide. This fact suggests that (+)-VII belongs to D-series. The NMR spectrum of VII could

TABLE 1. NMR SPECTRUM OF DIDEOXY-LACTONE (VII) (60 MHz in DMSO-d_6)

Proton	Multiplicity	δ (ppm)	J (Hz)
$C_{(2)}$-H	double d	2.21	J_{2-3} 1.5
$C_{(2)}$-H′	double d	2.84	$J_{2'-3}$ 5.3
$C_{(3)}$-H	m	4.25	$J_{2-2'}$ 17
$C_{(3)}$-OH	d	5.19	J_{3-4} 3.6
$C_{(4)}$-H	o	4.5	J_{3-OH} 4.5
$C_{(5)}$-H_3	d	1.25	J_{4-5} 6.3

d=doublet; m=multiplet; o=octet.

be analyzed employing decoupling technique (Table 1). The coupling constants between hydrogen atoms attached to the lactone ring (J_{2-3}, $J_{2'-3}$, J_{3-4}) could be explained most satisfactory on the assumption that dideoxylactone (VII) belongs to *threo*(*cis*)-series and D-form of VII holds a conformation and configuration shown in Fig. 1. All of the conformation derived from

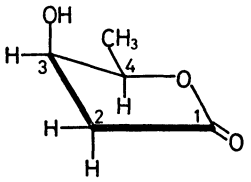


Fig. 1. Probable configuration and conformation of 2,5-dideoxy-D-*threo*-pentono-γ-lactone (D-VII).

erythro(*trans*)-configuration of VII gave no relevant explanation of the coupling constants. An examination of the Dreiding model of conformer shown in Fig. 1 indicates that the dihedral angles (ϕ) between neighboring hydrogen atoms should be as follows: $\phi_{2,3}$ 85—90°, $\phi_{2',3}$ 35—40°, and $\phi_{3,4}$ 40—50°. The calculation of J-values according to the method of Karplus[14] using modified J_0-value[15] and the estimated dihedral angles was performed. A fairly good agreement between observed and calculated J-values was obtained. The calculated J-values were found to be J_{2-3}=−0.28—−0.21, $J_{2'-3}$=5.94—5.2, and J_{3-4}=5.1—3.6. The unusual large dihedral angle between neighboring hydrogen atoms of *cis*-configuration in five membered ring ($\phi_{3,4}$ 40—50°) has been observed also in sugar derivatives.[15-17] Considering the presence of bulky methyl group in equatorial position and the planar shape of lactone grouping (C–CO–O–C),[18] the conformation illustrated in Fig. 1 seems to be highly probable.

The assignment of NMR spectrum of bromolactone (III) is summarized in Table 2, though there remains some uncertainty owing to poor resolution of the signals of $C_{(3)}$–H and $C_{(4)}$–H and overlap of the signal of water with them. The closely related coupling constants of bromolactone (III) with those of dideoxy-lactone (VII) indicate that D-bromolactone (D-III) has a similar conformation to D-VII shown in Fig. 1.

TABLE 2. NMR SPECTRUM OF BROMOLACTONE (III) (60 MHz in D_2O)

Proton	Multiplicity	δ (ppm)	J (Hz)
$C_{(2)}$-H	double d	2.57	J_{2-3} 1.5
$C_{(2)}$-H′	double d	3.12	$J_{2'-3}$ 5.3
$C_{(3)}$-H	m	*ca.* 4.7	$J_{2-2'}$ 18.5
$C_{(4)}$-H	sextet. (?)	*ca.* 4.85	J_{3-4} 3.8(?)
$C_{(5)}$-H	d	3.67	J_{4-5} 6.4

d=doublet; m=multiplet.

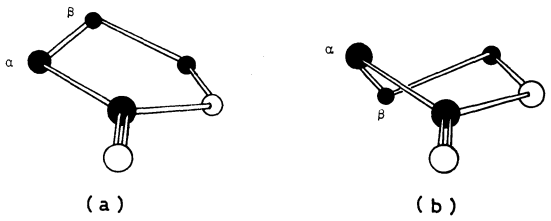


Fig. 2. Stable conformations of γ-lactone.

Mathieson[18] has pointed out that the stable conformation of γ-lactone is restricted to (a) and (b) in Fig. 2 in which C_β is either above or below the lactone plane owing to the preference of co-planarity of the five atoms of lactone group (C–CO–O–C). The location of C_β with respect to the lactone plane is related to the configuration at C_α. Considering the stable conformation of γ-lactone, a general rule has been proposed by Beecham[19] on the relation of the sign of Cotton effect of circular dichroism of $n\rightarrow\pi^*$ region of γ-lactone such as aldonolactone to the conformation of lactone ring. He has concluded that the sign of circular dichroism of aldono-γ-lactone is governed by the conformation of lactone ring independent on the configuration of substituent group other than C_α-position, and the conformation (a) and (b) are associated respectively with (+)- and (−)-Cotton effect. The lactones III and VII have no substituent

13) For example, F. H. Newth, W. G. Overend, and L. F. Wiggins, *J. Chem. Soc.*, **1947**, 10; P. W. Kent, M. Stacey, and L. F. Wiggins, *ibid.*, **1949**, 1232; N. K. Kochetkov, L. I. Kudryashow, A. I. Usov, and B. A. Dmitriev, *J. Gen. Chem. USSR*, **31**, 3081 (1961).

14) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

15) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *J. Chem. Soc.*, **1962**, 3699.

16) L. D. Hall, *Chem. Ind.*, **1963**, 950.

17) For review, see, L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

18) A. McL. Mathieson, *Tetrahedron Lett.*, **1963**, 81.

19) A. F. Beecham, *Tetrahedron Lett.*, **1968**, 2355, 3591.

Table 3. CD and ORD spectra of D-III, D-VII, and L-IV

	ORD in H_2O [ϕ]	CD in H_2O $\Delta\varepsilon_{max}$
D-III	max: 220 nm, +2940°; min: 213 nm, +2820°	213 nm, +0.480
D-VII	max: 222 nm, +2560°; min: 210 nm, +2130°	213 nm, +0.502
L-IV	max: 222 nm, +1370°; min: 199 nm, −1480°	210 nm, +0.597

group at C_α, however, as stated above, D-III and D-VII seem to hold conformation (a). Consequently, D-III and D-VII should exhibit (+)-Cotton effect in their circular dichroism spectra. As is shown in Table 3, the observed results agreed with the anticipation affording a further evidence for the conformation of D-III and D-VII.

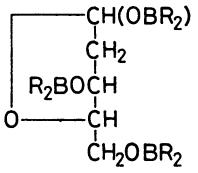
Treatment of bromolactone (III) with aqueous 1N potassium hydroxide at room temperature followed by standing at pH 1 for 24 hr afforded 2-deoxy-*erythro*-pentono-γ-lactone (IV) as a syrup in fairly high yield (63%). The syrupy γ-lactone (IV) was proved to be free from impurity on the basis of tlc, paper chromatography and NMR spectroscopy. The IR spectrum of IV and the elemental analysis of its phenylhydrazide were found to be consistent with the assigned structure. Although the syrupy IV derived from D- and L-bromolactones (III) showed somewhat lower $[\alpha]_D$-values as compared with a reported value,[20] the syrupy D- and L-IV could be used without purification in the subsequent reaction. D(+)-III and L(−)-III afforded L(−)-IV and D(+)-IV, respectively. Positive Cotton effect observed in the ORD and CD spectra of L(−)-IV (Table 3) indicates that L(−)-IV has conformation (a) in Fig. 2. Both of the bulky groups in IV, the hydroxyl group at $C_{(3)}$ and the hydroxymethyl group at $C_{(4)}$, take axial position in the conformation (a). An analogous rather unusual situation has been found in the conformation of D-ribono-γ-lactone.[21] The NMR spectrum of IV is recorded in Table 4. A confirmative information could not be obtained from the NMR data owing to the overlap of signal of $C_{(3)}$–H with that of $C_{(4)}$–H. The value of $J_{2'-3}$ is consistent with the conformation (a), however, the value of J_{2-3} is larger than the expected one. Accordingly, the possibility of the presence of a small fraction of conformation (b) can not be excluded. Inspection of the Dreiding model of conformation (b) revealed that the dihedral angles should be $\phi_{2,3}$ 160° and $\phi_{2',3}$ 35°. The coupling constants calculated using these angles are found to be as follows: J_{2-3} 8.87 and $J_{2'-3}$ 5.94.

Table 4. NMR Spectrum of 2-deoxy-*erythro*-pentono-γ-lactone (IV) (60 MHz in DMSO-d_6)

Proton	Multiplicity	δ (ppm)	J (Hz)	
$C_{(2)}$–H	double d	2.19	J_{2-3}	2.5
$C_{(2)}$–H′	double d	2.83	$J_{2'-3}$	6
$C_{(3)}$–H	broad m	4.26	$J_{2-2'}$	18
$C_{(4)}$–H			J_{4-5}	3.8
$C_{(3)}$–OH	d	5.43	J_{3-OH}	4
$C_{(5)}$–H_2	double d	3.54		
$C_{(5)}$–OH	t	5.0	J_{5-OH}	5.3

d=doublet, t=triplet, m=multiplet.

Reduction by means of sodium borohydride has been widely used for the conversion of aldono-γ-lactone to the corresponding aldose. However, treatments of 2-deoxy-lactone (IV) with the hydride under the usual conditions resulted in the recovery of IV. In view of the ease of reduction of α-hydroxy- and α-amino-esters to aldehydes,[22] the unsuccessful reduction of IV seems to be attributable to the absence of such substituent at α-position of IV. The reduction of IV could be achieved by the use of bis(1,2-dimethylpropyl)-borane (disiamylborane) which has been proposed by Brown and Bigley.[23] The reagent has been successfully applied for acylated aldono-lactones by Kohn, Samaritano, and Lerner.[24] The syrupy IV in anhydrous tetrahydrofuran was mixed with a large excess of disiamylborane. After the mixture had been stood over *ca.* 20 hr at room temperature, water was added to decompose the excess of reducing agent and to hydrolyze the borinate ester (XII) presumably formed. The



(XII)

R=-CH(CH$_3$)·CH(CH$_3$)$_2$

aqueous mixture was extracted with ether to remove dialkylborinic acid. Evaporation of the resulting aqueous layer afforded a syrup. Tlc of the syrup gave a spot which exactly corresponds to that of an authentic sample of 2-deoxy-*erythro*-pentose (V), and no other distinct spots could be observed. Treatment of the syrupy V with aniline according to the usual procedure[25] gave crystalline aniline derivative (61% based on lactone, IV). D-, L-, and DL-anilides thus prepared gave superimposable IR spectra with that of the anilide prepared from an authentic 2-deoxy-D-*erythro*-pentose. As summarized in Table 5, good coincidence of the melting points and specific rotations with those of reported values were found. The anilide (VI) yielded 2-deoxy-*erythro*-pentose (V) in a high yield (*ca.* 90%)

20) R. E. Deriaz, W. G. Overend, M. Stacey, E. G. Teece, and L. F. Wiggins, *J. Chem. Soc.*, **1949**, 1879.

21) R. J. Abraham, L. D. Hall, L. Hough, K. A. McLauchlan, and H. J. Miller, *ibid.*, **1963**, 748.

22) O. Baeyer, "Methoden der Organischen Chemie," (Houben-Weyl), Bd. 7, Teil 1, Georg Thieme Verlag, Stuttgart (1954), p. 279.

23) H. C. Brown and D. B. Bigley, *J. Amer. Chem. Soc.*, **83**, 486 (1961); H. C. Brown, D. B. Bigley, S. K. Arora, and M. M. Yoon, *ibid.*, **92**, 7161 (1970).

24) P. Kohn, R. H. Samaritano, and L. M. Lerner, *ibid.*, **86**, 1457 (1964); **87**, 5475 (1965).

25) E. Hardegger, "Methods in Carbohydrate Chemistry," Vol. 1, ed. by R. L. Whistler and M. L. Wolfrom, Academic Press, New York and London (1962), p. 177.

Table 5. Melting points and specific rotations of V and VI

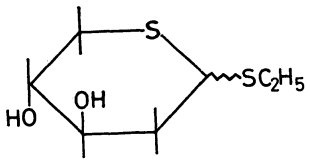
		Found	Lit. values
Mp	D-VI	170—173°C (decomp.)	170—172°C (decomp.)[26]
	L-VI	174—176°C (decomp.)	174—175°C[27]
	DL-VI	158—159°C (decomp.)	154—155°C[28]
$[\alpha]_D^{a)}$	D-VI	+56°	+46°[25,29]; +64°[30]
	L-VI	−55°	−58°[27]
$[\alpha]_D^{b)}$	D-V	−56°	−56°[30,31]; −57～−58°[25]
	L-V	+60°	+59°[20]

a) The value at equilibrium in pyridine.
b) The value at equilibrium in water.

on treatment with benzoic acid, benzaldehyde and water according to the usual procedure.[25] 2-Deoxy-D- and L-*erythro*-pentose (D- and L-V) initially obtained as syrup crystallized on standing for a few days. On the other hand, syrupy DL-V could be crystallized only after seeding with a small piece of crystal of an authentic D-V. 2-Deoxy-*erythro*-pentoses (D-, L-, and DL-V) showed no definite melting points indicating that they are mixture of α- and β-anomers. Tlc of crystalline 2-deoxy-*erythro*-pentoses gave spots just corresponding to that of authentic specimen. Also as recorded in Table 5, the specific rotations of D- and L-V were found to be identical with those of literature values. As a matter of course, D- and L-IV afforded D- and L-V, respectively. It should be noted that all the reactions proceed stereoselectively without any detectable formation of 2-deoxy-*threo*-pentose, an epimer of V. In view of the quite different physical properties of 2-deoxy-*threo*-pentose [D-isomer: $[\alpha]_D^{19}=-2°$ (H_2O)[32]] and its anilide [D-isomer: mp 137°C, $[\alpha]_D^{19}=-20°$ (H_2O);[32] DL-isomer: mp 145—146°C[28]] and the homogeneous nature of syrupy V as revealed by tlc, the formation of epimeric 2-deoxy-*threo*-pentose can be ignored. The over-all yields of DL-, L-, and D-V were found to be 9.3, 3.8, and 3.0%, respectively.

Independently and about the same time with the publication of preliminary report of the present study,[4] reduction of free aldonolactone to aldose by means of disiamylborane was reported.[33] The present authors have carried out the reduction of DL-bromolactone (III) and DL-dideoxy-lactone (VII) by the use of disiamylborane. DL-Dideoxy-lactone (VII) yielded 2,5-dideoxy-DL-*threo*-pentose (VIII) as a syrup. The syrup gave a strong spot on tlc accompanied by a few very weak spots. The syrup was converted to 2,4-dinitrophenylhydrazone (48% based on VII) which gave satisfactory elemental analysis and IR spectrum. Reduction of DL-bromolactone (III) afforded syrupy 5-bromo-2,5-dideoxy-DL-*threo*-pentose (IX). The syrupy IX was converted to crystalline diethylmercaptal (X, 38% based on III). Hydrolysis of X gave crystalline DL-IX. Bromopentose (IX) was found to be very unstable and decomposed at room temperature in a few days forming a black material. Mercaptal (X) was also rather unstable compound, but could be kept without decomposition in a refrigerator.

Because bromopentose (IX) seemed to be a potential precursor of aminopentose, bromomercaptal (X) was treated with sodium azide in boiling methanol to give 5-azido-compound (XI). After 30 hr, tlc of the reaction product gave no spot of bromomercaptal (X), but exhibits two main spots together with two minor spots. 5-Azido-compound (XI) could be obtained from one of the minor spot in a poor yield (9%). Conversion of XI to aminopentose had to be abandoned owing to the poor yield. The substances obtained from the two main spots gave no characteristic absorption other than hydroxyl group in their IR spectra. The same substances were obtained when bromomercaptal (X) was refluxed in methanol in the presence of sodium hydrogen carbonate. Therefore, the substances presumably concern with the anomer mixture of XIII.[34]

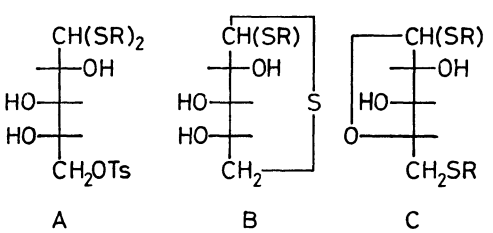


(XIII)

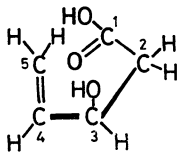
Treatment of bromomercaptal (X) with ammonia resulted in the formation of complex mixture and definite compound could not be identified.

Finally, we wish to give a brief account on the nature of stereoselectivety of the above-mentioned reactions.

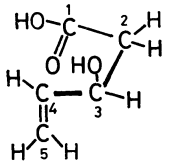
26) H. W. Diehl and H. G. Fletcher, Jr., *Arch. Biochem. Biophys.*, **78**, 386 (1958).
27) K. Butler, S. Laland, W. G. Overend, and M. Stacey, *J. Chem. Soc.*, **1950**, 1433.
28) F. Weygand and H. Leube, *Chem. Ber.*, **89**, 1914 (1956).
29) J. C. Sowden, *J. Amer. Chem. Soc.*, **76**, 3541 (1954).
30) L. Hough, *J. Chem. Soc.*, **1953**, 3066.
31) W. G. Overend, M. Stacey, and L. F. Wiggins, *ibid.*, **1949**, 1358.
32) F. Weygand, Ref. 25), p. 185.
33) T. A. Giudici and A. L. Fluharty, *J. Org. Chem.*, **32**, 2043 (1967). Other instances of disiamylborane reduction of aldonolactone derivatives, see, P. Kohn, L. M. Lerner, A. Cahn, Jr., S. D. Ginodrio, and C. A. Zitrin, *Carbohyd. Res.*, **7**, 21 (1968) and references cited therein.
34) Recently, J. Harness and N. A. Hugher (*Chem. Commun.*, **1971**, 811) have reported the formation of furanose derivative (C) instead of cyclic sulfide (B) on heating an acetone solution of 5-*O*-*p*-toluenesulfonyl-L-arabinose diethyl or dibenzyl dithioacetal (A, R=Et or benzyl). Consequently, the possibility that the substance obtained from bromoacetal (X) has a structure analogous to C can not be excluded. Further investigation about this point is now in progress.



As previously described, reaction of β-hydroxy-γ,δ-ethylenic acid (I) with *N*-bromosuccinimide in water gave exclusively *threo*-isomer (III) and unexpectedly the formation of epimeric *erythro*-isomer could not be observed. Beacuse the intramolecular nucleophilic attack of carboxyl group has been recognized in the electrophilic addition reaction of γ,δ-ethylenic acid,[35] bromo-γ-lactone (III) may be formed directly by the participation of carboxyl group without intermediacy of bromo-dihydroxy acid. Therefore, it seems to be likely that hydroxy-ethylenic acid (I) holds preferentially the conformation XIV or XV in which the



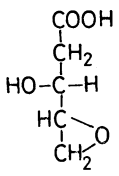
(XIV)



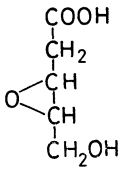
(XV)

carboxyl group situates in a proximity of the ethylenic bond. The hydroxyl group at $C_{(3)}$ and $C_{(5)}$ in conformation XIV are located in the same side with respect to the plane defined by $O-C_{(1)}-C_{(2)}-C_{(3)}-C_{(4)}$. On the contrary, the hydroxyl groups at $C_{(3)}$ and $C_{(5)}$ in conformation XV are situated in opposite side of the plane. Consequently, an additional stability would be rendered to the conformer XIV, because a hydrogen bonding between the hydroxyl group at $C_{(3)}$ and π-electron of the ethylenic bond[36] is possible only in XIV. If hydroxy-ethylenic acid (I) has the conformation XIV and bromonium ion attacks $C_{(5)}$ from the back side of carboxyl group being accompanied by simultaneous attack of carboxyl oxygen to $C_{(4)}$, the resulting bromolactone (III) should have *threo*-configuration.

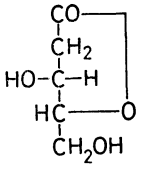
threo-Bromolactone (III) affords solely *erythro*-lactone (IV) without contamination of *threo*-isomer by the reaction with an aqueous potassium hydroxide followed by acid. This fact indicates that the ring opening of *threo*-epoxide (XVI) which is a possible reaction intermediate should occur at $C_{(4)}$ instead of $C_{(5)}$ with complete inversion of configuration. This is in accord with the general tendency of ring opening of epoxide, *i.e.*, usually epoxide ring is cleaved by acid at secondary carbon with inversion of configuration.[37] However, such a clear-cut result observed in the conversion of III into IV is rather unusual in saturated aliphatic epoxides. An intramolecular participation of carboxyl group again might have an important role in this reaction, *i.e.*, the carboxyl oxygen in XVI preferentially attacks $C_{(4)}$ to give γ-lactone (IV) rather than $C_{(5)}$ which leads to the formation of δ-lactone. The complete inversion at $C_{(4)}$ seems to be attributable to



(XVI)



(XVII)



(XVIII)

the intramolecular nature of attack and the rather high nucleophilicity of carboxyl group. The possibility of formation of epoxide (XVII) as a reaction intermediate which might be formed from XVI by the attack of hydroxyl group at $C_{(3)}$[38] can be ruled out, because the ring opening at either $C_{(3)}$ or $C_{(4)}$ of *erythro*-type XVII should result in the formation of 2-deoxy-*threo*-pentono-γ-lactone (XVIII) being in conflict with the observation. Therefore, it can be concluded that the configuration of $C_{(3)}$ in hydroxyethylenic acid (I) is kept intact throughout the reaction sequence. Accordingly, *R*-configuration of (−)-hydroxyethylenic acid [(−)-I] which gave 2-deoxy-L-*erythro*-pentose (L-V) and *S*-configuration of (+)-ethylenic acid [(+)-I], the precursor of 2-deoxy-D-*erythro*-pentose (D-V) are concluded.

Experimental

Melting points were measured on a Mettler EP2 apparatus and uncorrected. The IR spectra were obtained on a Hitachi EPI-2, EPI-S or a JACSO DS-402G spectrophotometer. The ORD and CD spectra were measured on a Yanagimoto ORD-185 and a JASCO ORD/UV-5 spectropolarimeters, and the NMR spectra, with a Varian A-60 or T-60, using tetramethylsilane or sodium 4,4-dimethylsilapentane sulfonate as internal standard. Double irradiation was performed on a JEOL JNM-4H-100 or JNM-C-60HL spectrometer. A commercial silica gel (E. Merck, Darmstadt, Germany, 70—325 mesh) was immersed in 60% aqueous acetic acid overnight and washed thoroughly with water until the filtrate gave a neutral test. After the washed silica gel had been kept at 120°C for 15 hr, it was used in the chromatography. Silica gel G (E. Merck, Darmstadt, Germany) was used as adsorbent in tlc. Benzene–ethyl acetate (1:1) (A), acetone (B), methanol (C) and ethyl acetate–95% ethanol (20:1) (D) were used as solvents. Iodine[39a] (a), hydroxamic acid reagent[39b] (b), Tollens' reagent[40] (c) and Dische's reagent[41] (d) were used as detection reagents. In the case of reagent (d), the sprayed glass was covered with another plate of glass and heated at 90—100°C to develop color reaction.

Ethyl 3-Hydroxy-4-pentenoate. In a nitrogen atmosphere, a 30 m*l* portion of a solution of ethyl bromoacetate (111 m*l*, 1 mol)[41] and acrolein (87 m*l*, 1.3 mol) in anhydrous benzene (250 m*l*) was added to zinc powder[43] (142 g, 2.17 g-atom)

35) See, for example, P. B. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, Amsterdam, London and New York (1966), p. 140.

36) M. Ōki and H. Iwamura, This Bulletin, **32**, 567 (1959).

37) Cf., E. L. Eliel, "Steric Effects in Organic Chemistry," ed. by M. S. Newman, John Wiley and Sons, Inc., New York (1956), p. 106.

38) On the neighboring-group participation of hydroxyl group under acidic conditions, see, L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967).

39) K. Randerath, translated by D. D. Libman, "Thin-layer Chromatography," Academic Press, New York and London (1963), a) p. 56, b) p. 203.

40) Reference 10, p. 869.

41) Z. Dische, *Mikrochemie*, **8**, 4 (1930).

42) S. Natelson and S. Gottfried, "Organic Syntheses," Coll. Vol. III, p. 381 (1955).

43) The quality of zinc powder is essential in this reaction. Only the zinc powder of Mitsuwa Chemicals Co. gave satisfactory result.

activated with hydrochloric acid[44] and the mixture was stirred under careful heating. After the initial vigorous reaction had subsided, the remaining solution was added to the stirred mixture under careful heating in such a rate to maintain gentle reflux. After the addition of solution had been completed, the mixture was refluxed for further 30 min under stirring. The hot reaction mixture was poured into an ice-cooled 4N sulfuric acid (600 ml) under stirring. Greyish viscous insoluble material was removed by filtration and washed with ether. The washings were combined with the organic layer. The aqueous layer was extracted 6 times with ether. The total organic layer was washed once with a saturated sodium chloride solution and twice with a saturated solution of sodium chloride containing sodium hydrogen carbonate and dried (sodium sulfate). The residue obtained by evaporation of the solvent under reduced pressure was distilled under nitrogen atmosphere *in vacuo*. Ethyl 3-hydroxy-4-pentenoate was obtained as colorless liquid, 72 g (50%), bp 63—64°C/2 mmHg, n_D^{25} 1.4393. IR (neat): 3470 (O–H); 1735 (C=O); 995, 925 (–CH=CH_2) cm^{-1}.

Found: C, 58.60; H, 8.33%. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39%.

When the reaction was carried out in other solvents of low boiling points such as ether, diisopropyl ether or tetrahydrofuran, the control of exothermic reaction was difficult resulting in a poor yield.

N-*Phenyl-3-hydroxy-4-pentenoamide.* According to the reported method,[45] ethyl hydroxy-pentenoate was converted to crystalline anilide. To an ice-cooled solution of ethylmagnesium bromide [from magnesium (2 g), ethyl bromide (10 g) and ether (60 ml)] was added aniline (8 g) and then the pentenoate (6 g) under stirring. After the mixture had been stirred for 30 min at room temperature and then further 30 min at 40°C, the reaction mixture was poured into 2N hydrochloric acid (50 ml). The crystals obtained upon work-up of the ethereal layer were recrystallized twice from benzene, thus yielding pure anilide as colorless needles, mp 127.5—128.5°C. IR (Nujol mull): 3300, 3210, 3140, 3080 (OH and NH); 1665 (amide I), 1550 (amide II), 1315 (amide III); 1603, 757, 690 (C_6H_5–) cm^{-1}.

Found: C, 69.14; H, 6.87; N, 7.27%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33%.

3-Hydroxy-4-pentenoic Acid (I). Ethyl 3-hydroxy-4-pentenoate (92.8 g, 0.644 mol) was added over a period of 45 min into an ice-cooled and stirred solution of potassium hydroxide (38.1 g, 0.68 mol) in water (635 ml). The mixture was stirred for 14 hr at room temperature and then stood over 12 hr at the same temperature. The reaction mixture was extracted 3 times with ether. The ice-cooled aqueous layer was made just acid to Congo red with concentrated hydrochloric acid (59 ml) and then saturated with sodium chloride. The aqueous layer was extracted 5 times with ether. The extract was washed 3 times with a saturated sodium chloride solution. The washings were combined with the aqueous layer and extracted with ether using a continuous extractor for 20 hr. The extract was washed according to the above-stated procedure. The total aqueous layer was again extracted by means of a continuous extractor for 20 hr. After washing procedure, the extract was combined with other ethereal extracts. The total extract was dried over sodium sulfate. The residue obtained by evaporating the solvent was distilled *in vacuo* under nitrogen atmosphere to give 3-hydroxy-4-pentenoic acid (I) as viscous colorless liquid, 63.5 g (85%), bp 95°C/1 mmHg, n_D^{30} 1.4630. IR (neat): *ca.* 3500—2500 (OH); 1715 (C=O); 995, 930 (–CH=CH_2) cm^{-1}.

Found: C, 51.56; H, 7.06%. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94%.

It was found that hydroxy-pentenoic acid (I) is easily dehydrated to give crystalline pentadienoic acid (II).[46] When the hydrolysis of I was carried out with 2N potassium hydroxide at room temperature for 2 days, II was obtained as main product.

Optical Resolution of 3-Hydroxy-4-pentenoic Acid (I). Hydroxy-pentenoic acid (I, 25.7 g, 0.222 mol) was added to a suspension of quinine (36 g, 0.111 mol) in hot water (295 ml) and shaken for a few min on a boiling water-bath. A slightly turbid solution thus obtained was treated with active charcoal. Crystals deposited mostly on standing the clear filtrate, otherwise the filtrate was seeded to cause crystallization. After standing in a refrigerator for 3 days, the crystals were collected by filtration and washed with water. The mother liquor was concentrated to one-half volume and stood over 8 days in a refrigerator, thus yielding second crop of crystals. The combined crystals (32 g) were recrystallized from water (295 ml), yielding colorless needles, 26.2 g, $[\alpha]_D^{24}=-137°$ ($c=1.1$, H_2O). The crystals showed no definite melting point, but most of the crystals melted at 117—122°C. The mother liquor of recrystallization gave second crop of crystals, 2.7 g, $[\alpha]_D^{18}=-134°$ ($c=1.1$, H_2O). The total yield was 57%. IR (Nujol mull): 1550, 1410 (–CO_2^-) cm^{-1}.

Found: C, 65.67; H, 7.54; N, 6.10%. Calcd for $C_{25}H_{32}O_5N_2 \cdot H_2O$: C, 65.48; H, 7.47; N, 6.11%.

The crystals lost its water of crystallization of heating to 65°C *in vacuo*, but the anhydrous crystals still showed no definite melting point (most of the crystals melted at 119—124°C).

Found: C, 67.92; H, 7.44; N, 6.33%. Calcd for $C_{25}H_{32}O_5N_2$: C, 68.16; H, 7.32; N, 6.36%.

Quinine salt monohydrate (25.1 g, 0.0548 mol) thus obtained was placed in a separatory funnel and mixed with sodium hydrogen carbonate (6 g, 0.071 mol), water (130 ml) and chloroform (500 ml). The mixture was shaken to dissolve the quinine salt. The organic layer was washed twice with water. The washings were combined with the aqueous layer and made just acid to Congo red with 6N hydrochloric acid under ice-cooling. The aqueous solution was treated according to the procedure used in the preparation of *rac*-hydroxy-pentenoic acid (I). (−)-I was obtained as pale yellow liquid, 4.6 g, (72%), $[\alpha]_D^{25}=-9.8°$ ($c=0.81$, H_2O). Ths material could be used without further purification in the subsequent reaction. A vacuum distillation of the crude material gave pure (−)-I as colorless viscous liquid, bp 107—109°C/3 mmHg, n_D^{20} 1.4658, $[\alpha]_D^{20}=-9.6°$ ($c=1.03$, H_2O), $[\alpha]_D^{17}=-26°$ ($c=1.35$, C_2H_5OH). Pure (−)-I crystallized in a refrigerator. The IR spectrum of (−)-I was found to be superimposable with that of racemic I.

Found: C, 51.57; H, 6.99%. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94%.

The initial mother liquor was concentrated to *ca.* 50 ml and mixed with sodium hydrogen carbonate (15 g). The crystals of quinine deposited were removed by filtration and washed with water. Partially resolved (+)-hydroxy-pentenoic acid, light yellow liquid, 12.8 g (50% recovery), $[\alpha]_D^{25}=+4.5°$ ($c=2.08$, H_2O) was obtained from the combined aqueous layer according to the previously described procedure. The specific rotation indicates that the optical

44) R. L. Shriner, "Organic Reactions," Vol. 1, John Wiley and Sons, Inc., New York (1942), p. 16.

45) D. V. N. Hardy, *J. Chem. Soc.*, **1936**, 398.

46) E. R. H. Jones, G. H. Whitham, and M. C. Whiting, *ibid.*, **1954**, 3201.

purity of the (+)-hydroxy-pentenoic acid should be 47%. In another run, partially resolved (+)-I having optical purity of 54% was obtained. Purified quinidine[47] (18.1 g, 0.056 mol) was mixed with partially resolved (+)-I [8.4 g, $[\alpha]_D=+14°$ (C_2H_5OH), optical purity=54%, corresponds to 0.056 mol of pure (+)-I] and water (25 m*l*). The mixture was heated to give a homogeneous solution. The solution was seeded with crystals of qunidine salt of I and kept at room temperature for 4 days. The crystals deposited were collected by filtration and washed with acetone. The crystals were recrystallized from acetone to give pure quinidine salt, colorless rods, 11.4 g (46%), $[\alpha]_D^{17}=+180°$ ($c=0.11$, H_2O). The crystals showed no definite melting point (130—149°C). IR (Nujol mull): 1594; 1404 ($-CO_2^-$) cm^{-1}.

Found: C, 68.00; H, 7.47; N, 6.32%. Calcd for $C_{25}H_{32}O_5N_2$: C, 68.16; H, 7.32; N, 6.36%.

Sodium hydrogen carbonate (2.5 g, 0.03 mol) was added to a solution of pure qunidine salt (11.4 g, 0.0259 mol) in water (40 m*l*). Quinidine initially deposited as liquid could be crystallized on seeding and removed by filtration. Treatment of the aqueous layer according to the procedure used in the preparation of (−)-I afforded slightly crude (+)-I as liquid, 2.8 g (93%), $[\alpha]_D^{17}=+26°$ ($c=1.01$, C_2H_5OH). The IR spectrum of this material was found to be superimposable with that of DL-isomer. This material was used in the following reaction without further purification. Vacuum distillation under nitrogen atmosphere of crude (+)-I obtained by another run yielded (+)-I as colorless liquid, bp 104—106°C/2 mmHg which crystallized on standing in a refrigerator, n_D^{25} 1.4633, $[\alpha]_D^{25}=+24°$ ($c=1.03$, C_2H_5OH).

Found: C, 51.13; H, 6.90%. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94%.

Second crop of qunidine salt was obtained from the aqueous mother liquor. Recrystallization of the crude salt from water gave 5.4 g of qunidine salt, $[\alpha]_D^{19}=+173°$ ($c=0.11$, H_2O).

Attempts to resolve (±)-I by means of cinchonine, cinchonidine, brucine, strychnine, and ephedrine gave fruitless results.

DL-*3-Acetoxy-4-pentenoic Acid.* A mixture of hydroxy-pentenoic acid (I, 24 g, 0.2 mol) and acetic anhydride (50 m*l*) was heated on a boiling water-bath for 2.5 hr. After the acetic anhydride and acetic acid formed had been removed under reduced pressure, water (40 m*l*) was added to the residue and kept at 60°C for 1 hr. The reaction mixture was saturated with sodium chloride and extracted with ether. The extract was dried over sodium sulfate. The residue obtained by evaporation of the solvent under reduced pressure was distilled *in vacuo* in a stream of nitrogen, yielding acetoxy-pentenoic acid as colorless liquid, 26.5 g (83%), bp 96.5—98°C/1.5 mmHg, n_D^{25} 1.4445, IR (neat): *ca.* 3600—2400 (OH): 1745, 1720 (C=O); 990, 935 ($-CH=CH_2$) cm^{-1}.

Found: C, 53.15; H, 6.34%. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37%.

Acetylation of I by means of pyridine-acetic anhydride gave predominantly pentadienoic acid.

5-Bromo-2,5-dideoxy-DL-, D-, *and* L-threo-*Pentono-γ-lactones (III).* A mixture of DL-β-hydroxy acid (I, 10.4 g, 0.09 mol), finely powdered *N*-bromosuccinimide[48] (17.7 g, 0.099 mol) and water (180 m*l*) was stirred at room temperature for 17 hr in a dark place. The resulting orange yellow clear solution was saturated with sodium chloride (55 g) and extracted with ether (50 m*l*×5). The ethereal extract was washed with a saturated sodium chloride solution containing 5% of sodium hydrogen sulfite (30 m*l*) and a saturated sodium chloride solution (20 m*l*×3), successively and dried (sodium sulfate). The residue obtained by evaporating the solvent under reduced pressure was placed in an evacuated desiccator containing phosphorus pentoxide. The yellowish brown syrup thus obtained (5.8 g) exhibited satisfactory IR spectrum and gave a strong spot of III at R_f 0.55 (solvent system: A, detection reagent: a or b) in the tlc accompanied with a faint coloration near the starting point.

The combined aqueous layer and washings were mixed with a saturated sodium chloride solution containing 5% of sodium sulfite (2 m*l*) to reduce liberated bromine and extracted with ether for 24 hr employing a continuous extractor. The ethereal extract containing crystals and oily material was chilled on an ice-bath. The crystals were collected by filtration and washed successively with ether and ethyl acetate which could be identified as succinimide on the basis of IR spectroscopy. Ethyl acetate was added to the combined filtrate and washings to dissolve separated oily material and dried (sodium sulfate). The residue obtained by evaporation of the solvent under diminished pressure was placed in an evacuated desiccator over phosphorus pentoxide, thus yielding second crop of yellow syrup (12.6 g). Because tlc (solvent system: A, detection reagent: a or b) of the syrup revealed that the main constituents of the syrup are bromolactone (III, R_f 0.55) and succinimide (R_f 0.4), the syrup (10 g) was subjected to a chromatography on silica gel (300 g) employing benzene–ethyl acetate (1: 1) as eluting solvent. The eluate was fractionated into 100 m*l* portions. Bromolactone (III, 5.2 g) contaminated with a small amount of succinimide was obtained from the fractions 3—10, which gave pure bromolactone (III, 3.34 g) on re-chromatography on silica gel. The total yield of pure III was found to be 57%, n_D^{20} 1.5214, IR ($CHCl_3$): 3610 (OH); 3460 (hydrogen bonded OH); 1795 (C=O) cm^{-1}. IR (neat): 3460 (hydrogen bonded OH); 1775 (C=O) cm^{-1}.

Found: C, 30.17; H, 3.92; Br, 40.72%. Calcd for $C_5H_7O_3Br$: C, 30.79; H, 3.62; Br, 40.97%.

A chromatography of the second crop of III on neutral alumina (Woelm, activity III) gave less satisfactory result.

Treatment of DL-bromolactone (III) in ethanol with phenylhydrazine gave phenylhydrazide which was recrystallized from ethanol to give pure material as colorless needles. The phenylhydrazide sintered at 135°C and decomposed at 137—138°C.

Found: C, 43.82; H, 5.04; N, 9.02; Br, 26.46%. Calcd for $C_{11}H_{15}BrN_2O_3$: C, 43.58; H, 4.99; N, 9.24; Br, 26.36%.

According to the procedure used in the preparation of DL-bromolactone (III), (−)-β-hydroxy-pentenoic acid [(−)-I, 7.275 g, 0.0627 mol], *N*-bromosuccinimide (12.3 g, 0.069 mol) and water (130 m*l*) gave D-bromolactone (D-III). The first crop [4.15 g, $[\alpha]_D^{25}=+45°$ (initial)→+44° (after 2 weeks) ($c=0.65$, H_2O)] gave an identical IR spectrum with that of pure DL-III and could be used in the following reaction without further purification. Chromatography of the second crop (9.89 g) on silca gel or neutral alumina afforded pure D-III. The total yield of pure D-III was 56%, n_D^{25} 1.5207, $[\alpha]_D^{25}=+54°$ (after 24 hr)→+50° (after 2 weeks) ($c=0.081$, H_2O).

Found: C, 30.95; H, 3.68; Br, 40.48%. Calcd for $C_5H_7O_3Br$: C, 30.79; H, 3.62; Br, 40.97%.

Phenylhydrazide of D-III was recrystallized from 2-propanol to give aggregate of colorless needles or plates, mp 132—135°C (decomp.) [with a pre-heated bath (115°C) and a rapid temperature increase, 6°C/min].

47) R. T. Major and J. Finkelstein, *J. Amer. Chem. Soc.*, **63**, 1368 (1941).

48) E. Campaigne and B. F. Tullar, "Organic Syntheses," Coll. Vol. IV, p. 921 (1963).

Found: C, 43.84; H, 5.06; N, 9.07; Br, 25.96%. Calcd for $C_{11}H_{15}BrN_2O_3$: C, 43.58; H, 4.99; N, 9.24; Br, 26.36%.

The reaction of (+)-hydroxy-pentenoic acid (2.8 g, 0.024 mol) with *N*-bromosuccinimide (4.7 g, 0.027 mol) in water (50 m*l*) afforded L-bromolactone (L-III). The first crop [1.54 g, $[\alpha]_D^{17}=-46°$ (initial)$\rightarrow[\alpha]_D^{20}=-46°$ (after 2 weeks) ($c=0.54$, H_2O)] could be used without purification in the subsequent reaction. The second and third crops (total 3.27 g) were subjected to chromatography on silica gel to give pure L-III. The total yield of pure L-III was found to be 2.47 g (52%).

2-Deoxy-DL-, L-, *and* D-erythro-*Pentono-γ-lactones (IV).* A mixture of DL-III (860 mg, 4.41 mmol) and 1N potassium hydroxide (9 m*l*, 9 mmol) in a tightly stoppered flask was swirled for 30 min in an ice-bath, and then kept at room temperature for 23 hr. The reaction mixture was treated with Amberlite IR 120 (H^+) to remove potassium ion and the resulting acid solution (pH *ca.* 1) was stood over 22 hr at room temperature. The solution was chilled on an ice-bath and treated with Dowex 3 (OH^-). The solution which gave negative Beilstein's test was concentrated under reduced pressure at a temperature below 30°C. The residue was placed in an evacuated desiccator containing phosphorus pentoxide, thus yielding 2-deoxy-DL-*erythro*-γ-lactone (DL-IV) as almost colorless syrup, 346 mg, (59%), n_D^{20} 1.4900, IR (neat): 3380 (OH); 1765 (C=O) cm^{-1}. The syrup gave one spot (R_f 0.58) on a paper chromatogram (solvent system: 1-butanol: acetic acid: water=4:1: 5,[47] detection reagent: silver nitrate-sodium hydroxide-ammonia,[49] filter paper: Toyo Roshi No. 51). Tlc (solvent: B, detection reagent: b or c) of the syrup gave a main spot at R_f 0.75 and in some cases very weak spots at R_f 0.6 and 0.42 were observed.

According to the usual manner, phenylhydrazide was obtained from the syrup (95 mg, 0.72 mmol) and phenylhydrazine (84 mg, 0.78 mmol) in ethanol (1 m*l*). The hydrazide was recrystallized from 2-propanol and then from acetone to give pure material, aggregate of colorless leaflets. The crystals were found to be a mixture of two dimorphic forms, mp 134—135°C and mp 140—142°C.

Found: C, 54.94; H, 6.73; N, 11.55%. Calcd for $C_{11}H_{16}O_4N_2$: C, 54.99; H, 6.71; N, 11.66%.

Treatment of D(+)-bromolactone (D-III, 260 mg, 1.33 mmol) according to the procedure used in the case of DL-isomer gave 2-deoxy-L-*erythro*-pentono-γ-lactone (L-IV, 109 mg, 62%) as a colorless syrup which showed a superimposable IR spectrum with that of DL-IV, n_D^{20} 1.4870, $[\alpha]_D^{15}=-8.5°$ (initial)$\rightarrow-9.8°$ (after 2 weeks) ($c=1.08$, H_2O). Phenylhydrazide obtained from L-IV also showed dimorphism, mp 122—123°C and mp 146—146.5°C [lit,[31] mp 145—146°C].

Found: C, 54.84; H, 6.66; N, 11.57%. Calcd for $C_{11}H_{16}O_4N_2$: C, 54.99; H, 6.71; N, 11.66%.

L(−)-Bromolactone (L-III, 1.5 g, 7.7 mmol) afforded 2-deoxy-D-*erythro*-pentono-lactone (D-IV, 647 mg, 63%), $[\alpha]_D^{20}=+4.9°$ (initial)$\rightarrow+6.8°$ (after 13 days) ($c=1.04$, H_2O). The spectrum of D-IV was found to be identical with that of DL-form.

2-Deoxy-N-*phenyl*-DL-, L-, *and* D-erythro-*Pentosylamine (VI).* A solution of bis(1,2-dimethylpropyl)borane was prepared according to the usual procedure from 2-methyl-2-butene (1.9 g, 27 mmol) in anhydrous tetrahydrofuran and a stock solution of diborane in the same solvent (concentration: 0.85 mmol/m*l*, 8 m*l*, 6.8 mmol). To the ice-cooled and stirred solution of bis(1,2-dimethylpropyl)borane was added a solution of slightly crude 2-deoxy-DL-*erythro*-pentono-γ-lactone (IV, 160 mg, 1.2 mmol) in anhydrous tetrahydrofuran (7 m*l*) in an atmosphere of nitrogen. Evolution of hydrogen was observed. After the mixture had been stirred at room temperature for 21 hr, water (30 m*l*) was added under cooling on an ice-bath, and then further stirring was continued for 40 min at room temperature. Ether was added to the reaction mixture and the ether layer was extracted twice with water. The second aqueous extract gave a negative test for the Dische's reagent.[42] The combined aqueous layer was extracted 3 times with ether. All ethereal layers were combined, and again extracted with water. Total aqueous layer was concentrated under reduced pressure at a temperature below 30°C. The resulting syrup was mixed with methanol and the solvent was removed under diminished pressure. This procedure was repeated 3 times. The syrup thus obtained was dried in an evacuated desiccator over phosphorus pentoxide. Tlc (solvent: B, detection reagent: d) of the pale yellow syrup thus prepared (154 mg) produced a strong spot at R_f 0.51 corresponding to that of an authentic D-V and a very weak spot at R_f 0.58. The syrup was mixed with an aniline solution (1.4 m*l*) prepared from aniline (1.8 m*l*), ethanol (15 m*l*) and water (7 m*l*), and the mixture was placed in a refrigerator. The crystals deposited were collected by filtration and washed successively with 50% aqueous methanol and ether, thus yielding fairly pure DL-VI as almost colorless needles, 153 mg (61% based on DL-IV). The crystals were recrystallized from ethanol to give pure DL-VI, colorless plates, mp 158—159°C (decomp.) (with a pre-heated bath (140°C)). The IR spectrum (Nujol mull) of DL-VI [3320, 3250 (OH, NH); 1605, 1500, 1445, 760, 695 (C_6H_5–) cm^{-1}] was found to be identical with that of an authentic D-VI.

Found: C, 62.98; H, 7.37; N, 6.55%. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69%.

Treatment of L-lactone (L-IV, 124 mg, 0.94 mmol) with 2-methyl-2-butene (1.7 g, 24 mmol) and the stock solution of diborane (6 mmol) according to the above-mentioned procedure resulted in L-VI (120 mg, 61% based on L-IV). Pure L-VI was obtained upon recrystallization from ethanol, mp 174—176°C (decomp.) (with a pre-heated bath (*ca.* 155°C) and a heating rate of 4°C/min), $[\alpha]_D^{14}$ ($c=1.28$, pyridine): −140° (after *ca.* 20 min); −81° (after 2 hr); −70° (after 7 hr); −55° (after 24 hr); −55° (after 29 hr). L-VI gave a superimposable IR spectrum (Nujol mull) with those of DL-VI and authentic D-VI.

Found: C, 63.21; H, 7.34; N, 6.69%. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69%.

D-Anilide (D-VI, 184 mg, 58%) was obtained from D-lactone (D-IV, 202 mg, 1.53 mmol), 2-methyl-2-butene (2.6 g, 37 mmol) and the stock solution of diborane (9 mmol). Slightly crude D-VI obtained was recrystallized from ethanol, thus yielding pure D-VI as colorless plates, mp 170—173°C (decomp.) (with a pre-heated bath (150°C) and a heating rate of 3—4°C/min), $[\alpha]_D^{20}$ ($c=1.02$, pyridine): +150° (after 10 min); +77° (after 4.5 hr); +56° (after 24 hr); +56° (after 28.5 hr). D-VI thus obtained showed an identical IR spectrum (Nujol mull) with that of an authentic D-VI.

Found: C, 63.19; H, 7.27; N, 6.62%. Calcd for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69%.

2-Deoxy-DL-, L-, *and* D-erythro-*Pentoses (V).* A mixture of slightly crude DL-anilide (DL-VI, 193 mg, 0.923 mmol), benzaldehyde (0.2 m*l*, 1.9 mmol), benzoic acid (19 mg) and water (5.8 m*l*) was placed in a tightly stoppered flask and stirred for 24 hr at room temperature. Disappearance of crystals was observed after 1.5 hr resulting in separation of an oily material. After the mixture had been extracted

49) S. M. Partridge, *Biochem. J.*, **42**, 238 (1948).

3 times with ether, the aqueous layer was evaporated under reduced pressure at a temperature below 35°C. The residue was placed in an evacuated desiccator containing phosphorus pentoxide to give colorless syrup (133 mg, 88%). The syrup mixed with a small amount of ethyl acetate crystallized completely upon seeding with a tiny piece of crystal of an authentic 2-deoxy-D-*erythro*-pentose (D-V). The crystals were recrystallized from ethyl acetate to yield pure D-V, aggregate of colorless needles or plates. Fluctuation of melting point of D-V between 85—91°C was observed. D-V thus prepared gave identical tlc with that of an authentic specimen of 2-deoxy-D-*erythro*-pentose (R_f 0.52, solvent: B, detection reagent: d; R_f 0.73, solvent: C, detection reagent: d).

Found: C, 44.67; H, 7.42%. Calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.52%.

Similar treatment of L-anilide (L-VI, 49 mg, 0.23 mmol) with benzaldehyde (0.05 m*l*) and benzoic acid (5 mg) in water (1.5 m*l*) afforded L-V as colorless syrup (32 mg). The syrup was triturated with a small amount of acetone–2-propanol (6: 1) and placed in a refrigerator. The colorless crystals deposited were filtered and washed successively with ethyl acetate and ether, thus yielding pure 2-deoxy-L-*erythro*-pentose (L-V, 26 mg, 84%), $[\alpha]_D^{15}$ (c=1.06, H_2O): +63° (after 19 min); +61.5° (after 26 min); +60° (after 1.25 hr); +60° (after 3 hr); +60° (after 4.75 hr). Tlc of L-V produced a spot (R_f 0.5, solvent: B, detection reagent: d) which exactly coincided with that of an authentic specimen of D-V.

Found: C, 44.76; H, 7.50%. Calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.52%.

D-Anilide (D-VI, 91 mg, 0.44 mmol) was treated according to the above described procedure with benzaldehyde (0.1 m*l*), benzoic acid (9 mg) and water (2.8 m*l*). 2-Deoxy-D-*erythro*-pentose (D-V) was obtained in a yield of 91% (53 mg), $[\alpha]_D^{23}$ (c=1.12, H_2O): −56° (after 50 min); −56° (after 1.5 hr).

Found: C, 44.68; H, 7.52%. Calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.52%.

2,5-Dideoxy-DL- *and* D-threo-*Pentono-γ-lactones (VII).* A mixture of DL-bromolactone (DL-III, 2.2 g, 0.011 mol), tri-*n*-butyltin hydride[50] (7.2 g, 0.025 mol) and anhydrous tetrahydrofuran (25 m*l*) was refluxed for 8 hr and then stood overnight at room temperature. The residue obtained by evaporation of the solvent under reduced pressure was mixed with water (50 m*l*) and petroleum benzine (bp 60—80°C, 15 m*l*). The benzine layer was washed with water (20 m*l*× 2). The aqueous layer was filtered and combined with the washings. The combined aqueous layer was washed with petroleum benzine. Total benzine layer was extracted twice with water. The extract was added to the combined aqueous layer and treated with a mixture of active charcoal and celite. The resulting clear solution was evaporated under reduced pressure at a temperature below 35°C. The residue was dried in an evacuated desiccator over phosphorus pentoxide to give colorless syrup, 1.1 g (85%). Tlc of the syrup produced a spot at R_f 0.2 (solvent system: A, detection reagent: a or b). Dideoxy-γ-lactone (VII) could be distilled *in vacuo*, bp 109°C/0.1 mmHg, n_D^{25} 1.4606 [lit,[51] bp 139—141°C/0.6 mmHg, n_D^{25} 1.4632], IR ($CHCl_3$): 3620, 3450 (OH); 1780 C=O) cm^{-1}.

Found: C, 50.91; H, 6.86%. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94%.

Phenylhydrazide of DL-VII was prepared according to the usual procedure and recrystallized from 2-propanol to give pure material, colorless plates, mp 120—122°C.

Found: C, 58.77; H, 7.23; N, 12.33%. Calcd for $C_{11}H_{16}O_3N_2$: C, 58.91; H, 7.19; N, 12.49%.

A mixture of D(+)-bromolactone (D-III, 2.04 g, 10.5 mmol), tri-*n*-butyltin hydride (6.7 g, 23 mmol) and anhydrous tetrahydrofuran (25 m*l*) was refluxed for 18 hr and then allowed to stand overnight at room temperature. Treatment of the reaction mixture according to the procedure used in the case of DL-isomer afforded dideoxy-D-*threo*-pentono-γ-lactone (D-VII), 1.14 g (93%), bp 107°C/0.3 mmHg, n_D^{20} 1.4583, $[\alpha]_D^{20}$=+57° (after 4 hr)→+58° (after 2 weeks) (c=0.98, H_2O). D-VII gave an identical IR spectra (neat or in $CHCl_3$) with those of DL-VII.

Found: C, 51.98; H, 7.01%. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94%.

2,5-Dideoxy-DL-threo-*pentose (VIII).* Reduction of DL-dideoxy-pentono-lactone (DL-VII, 485 mg, 4.18 mmol) by means of bis(1,2-dimethylpropyl)borane prepared from 2-methyl-2-butene (6.4 g, 92 mmol) and a tetrahydrofuran solution of diborane (23 mmol) according to the procedure used in the reduction of 2-deoxy-pentono-lactone (IV) afforded DL-2,5-dideoxy-pentose (DL-VIII) as pale yellow syrup (575 mg). This substance reduced the Tollens' reagent and gave a positive test for the Dische's reagent.[40] Tlc (solvent system: D) of the syrup gave main spot at R_f 0.48 accompanying faint spots at R_f 0.68, 0.42, 0.34, and 0.18 (detection reagent: C). Only the main spot (R_f 0.48) could be observed when detection reagent d was used.

The syrupy DL-dideoxy-pentose (DL-VIII, 60 mg) was mixed with ethanol (1 m*l*) and a few small crystals of 2,4-dinitrophenylhydrazine was added to the refluxing solution, and when the crystals had dissolved, an additional small amount of the hydrazine was added to the solution. This procedure was repeated until no more dissolution of the hydrazine could be observed. Further reflux was continued (total 3 hr), and then the mixture was cooled. The resulting crystals were filtered and washed with ethanol. The filtrate gave second crop of crystals on addition of water. The crude crystals thus obtained (62 mg, 48% based on lactone, VII) were recrystallized successively from ethanol and ethyl acetate to give pure 2,4-dinitrophenylhydrazone of VIII, tiny yellow plates, mp 144.5—146.5°C. IR (KBr-disk): 3300, 3090 (OH, NH); 2970 (CH_3–); 1520, 1330 (–NO_2) cm^{-1}.

Found: C, 44.02; H, 4.90; N, 18.80%. Calcd for $C_{11}H_{14}O_6N_4$: C, 44.30; H, 4.73; N, 18.79%.

5-Bromo-2,5-dideoxy-DL-threo-*pentose Diethyl Dithioacetal (X).* The reaction of DL-bromolactone (DL-III, 585 mg, 3 mmol) with bis(1,2-dimethylpropyl)borane prepared from 2-methyl-2-butene (4.6 g, 66 mmol) and diborane (15.5 mmol) in tetrahydrofuran according to the method used in the case of 2-deoxy-pentono-lactone (IV) afforded a colorless syrup which gave positive test for the Dische's reagent (first crop: 427 mg; second crop was obtained from the ether extract containing disiamylborinic acid by extraction with water: 127 mg). The syrup (first crop, 255 mg) was mixed with ethanethiol (0.3 m*l*) and concentrated hydrochloric acid (1 m*l*) at room temperature resulting in instantaneous deposition of crystals with evolution of heat. After the mixture had been shaken for 15 min in an ice-bath, the slurry was mixed with water and the crystals were collected by filtration, washed thoroughly with water until neutral filtrate was obtained, and then washed with petroleum benzine, thus yielding thioacetal (X, 191 mg) as colorless needles. The second crop of syrup was treated according to the above

50) M. Ohara and R. Okawara, *J. Organometal. Chem.*, **3**, 484 (1965).

51) E. E. van Tamelen, F. M. Strong, and U. C. Quarck, *J. Amer. Chem. Soc.*, **81**, 750 (1959).

described procedure to give 20 mg of X. Total yield of X was 38% (based on III). Recrystallization of the crystals from petroleum benzine yielded pure X as white silky needles, mp 92.5—95°C (decomp.) (with a pre-heated bath (85°C) and a heating rate of 2°C/min), NMR ($CDCl_3$): δ 1.28 (6H, triplet, $J_{CH_3-CH_2}$ 7.6, CH_3). IR (KBr-disk): 3360 (OH); 2960 (CH_3–); 1415 (S–CH_2–) cm^{-1}.

Found: C, 35.81; H, 6.40; Br, 26.66; S, 21.13%. Calcd for $C_9H_{19}O_2BrS_2$: C, 35.64; H, 6.31; Br, 26.34; S, 21.14%.

5-Bromo-2,5-dideoxy-DL-threo-*pentose (IX).* DL-Thioacetal (DL-X, 97 mg, 0.32 mmol) in acetone (1 m*l*) and mercuric chloride (349 mg, 1.28 mmol) in acetone–water (1.5—0.2 m*l*) were mixed at room temperature with finely powdered cadmium carbonate (349 mg, commercial material had been washed with water and dried). After the mixture had been stirred for 24 hr, the insoluble material was removed by filtration and washed with acetone. The combined filtrate and washings were evaporated under reduced pressure in the presence of a small amount of cadmium carbonate. The residue was extracted 3 times with water (total 5 m*l*). The extract was treated with a mixture of Amberlite IR 120 (H^+) and Dowex 3 (OH^-) under ice-cooling. The ion exchange resins were removed by filtration and washed thoroughly with water. Concentration of the combined filtrate and washings *in vacuo* at a temperature below 35°C yielded a syrup. The syrup was dried in an evacuated desiccator over phosphorus pentoxide. The dried syrup (39 mg, 62%) was triturated with a small amount of ethyl acetate and kept in a refrigerator, resulting in complete crystallization. The crystals were recrystallized from ethyl acetate to give pure bromo-dideoxy-DL-*threo*-pentose (DL-IX) as colorless fine needles, mp 81.5—83.5°C (decomp.).

Found: C, 30.28; H, 4.49; Br, 41.76%. Calcd for $C_5H_9O_3Br$: C, 30.48; H, 4.60; Br, 40.56%.

DL-IX was found to be fairly unstable and in certain cases decomposition of DL-IX at room temperature to form black material was observed in a day.

5-Azido-2,5-dideoxy-DL-threo-*pentose Diethyl Dithoiacetal (XI).* A mixture of bromo-pentose mercaptal (X, 50 mg, 0.17 mmol) in methanol (5 m*l*) and sodium azide (87 mg, 1.3 mmol) in water (1.5 m*l*) was refluxed for 48 hr. The reaction mixture was evaporated under reduced pressure. The residue was mixed with methanol and again the solvent was removed *in vacuo*. This procedure was repeated to remove water completely. The residue thus obtained was extracted thoroughly with ethyl acetate. The residue obtained by evaporation of the solvent under reduced pressure was placed in an evacuated desiccator containing phosphorus pentoxide to give pale yellow syrup (30 mg). Preparative tlc of the syrup [silica gel G, thickness 0.5 mm; solvent system: chloroform–acetone (9: 1); detection reagent: iodine] resulted in the separation of the following substance: (a) R_f 0.6, almost colorless syrup, 8 mg, (b) R_f 0.35, colorless syrup, 11 mg, (c) R_f 0.17, colorless syrup, 4 mg (9%), IR (neat): 2100 ($-N_3$) cm^{-1}, (d) R_f 0.04, pale yellow syrup, 2 mg.

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