Syntheses of L-Threose and Methyl Di-*O*-acetyl-L-threuronate from *dextro*-Tartaric Acid

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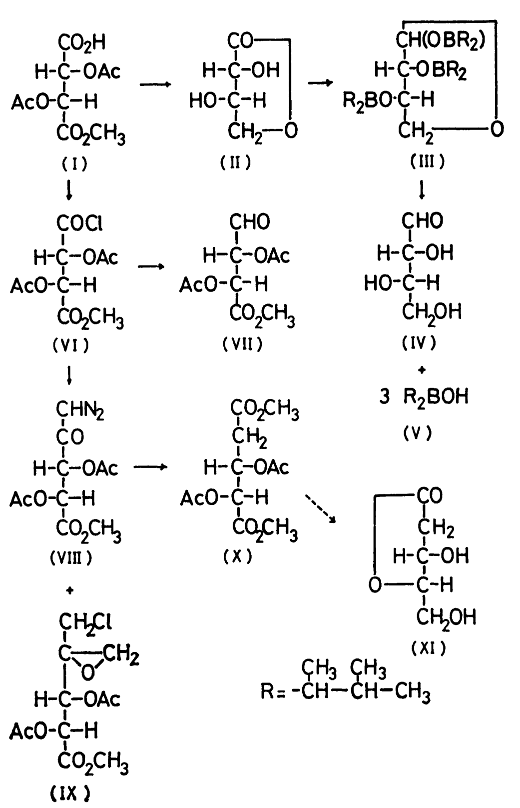
Reduction of methyl hydrogen di-*O*-acetyl-*dextro*-tartrate (I) with sodium borohydride in water afforded L-threono-γ-lactone (II). L-Threose (IV) was obtained on treatment of the γ-lactone (II) with an excess of disiamylborane. Reduction of ester chloride of di-*O*-acetyl-*dextro*-tartaric acid (VI) with tri-*n*-butyltin hydride yielded methyl di-*O*-acetyl-L-threuronate (VII). Attempts to reduce 2-deoxy-pentarate ester (X) derived from ester chloride (VI) *via* diazoketone (VIII) with sodium borohydride to give 2-deoxy-*threo*-pentono-γ-lactone (XI) gave unsatisfactory results. Formation of methyl L-*threo*-2,3-di-*O*-acetyl-5-chloro-5-deoxy-4-*C*-hydroxymethyl-4,4′-anhydropentonate (IX) in addition to diazoketone (VIII) was observed when ester chloride (VI) was treated with an excess of diazomethane. On the basis of the observed (—)-Cotton effect in the 290 nm region of ORD and CD spectra of L-threose (IV) and D-erythrose, possibility of the presence of an open chain non-hydrated *aldehyde*-form of aldotetrose in water was discussed.

dextro-Tartaric acid has been used widely as a starting material for syntheses of carbohydrates and their derivatives. L-Threuronate derivative (VII) was prepared by the Rosenmund reduction of ester chloride of *dextro*-tartaric acid derivative (VI).[1] Further reduction of VII with sodium amalgam afforded L-theritol *via* L-threonic acid.[1] Syntheses of L-threonolactone (II) and L-threuronate derivative (VII) have been achieved by the reduction of VI with tri-*tert*-butoxyaluminohydride.[2] The conversion of *dextro*-tartaric acid into L-apiose has been reported by Weygand and Scmiechen.[3]

We describe here some experiments to synthesize sugars and derivatives starting from *dextro*-tartaric acid carried out with the purpose of exploring the utility of complex hydride in carbohydrate chemistry.



It has been recognized that uronate esters could be reduced with sodium borohydride, in contrast to the failure of reduction of usual esters.[4] Treatment of monoethyl ester of *dextro*-tartaric acid with a large excess of sodium borohydride in anhydrous ethanol resulted in a partial recovery of the monoester accompanied by *dextro*-tartaric acid, hydrolysate of the ester. However, methyl hydrogen di-*O*-acetyl-*dextro*-tartrate (I) could be reduced to L-threono-γ-lactone (II) on treatment with sodium borohydride in water. The product obtained by the reaction of I (1 mol) with sodium borohydride (3.5 mol) in water was hydrolyzed without isolation with potassium hydroxide. Distillation of the hydrolysate *in vacuo* yielded crystalline L-threono-γ-lactone (II) in a 74% yield. Reduction of I could not be observed with the hydride in ethanol. The hydride in a mixture of ethanol and water afforded II in a low yield (47%). Facile reduction of I can reasonably be attributed to an enhanced electrophilicity of methoxycarbonyl funciton caused by the introduction of electron withdrawing acetyl groups.[5] The present procedure of reduction of *dextro*-tartaric acid derivative (I) is more convenient and more practical than the older procedures[1,2] and L-threono-γ-lactone (II) can be obtained in a much higher yield.

Sodium borohydride reduction of aldono-γ-lactone to aldose proposed by Wolfrom and his co-workers[6] has been applied successfully to various aldonic acid lactones.[7] Usually, the reduction is performed in a weakly acidic buffer solution to avoid hydrolysis of the lactone ring. The reduction of II with an excess of

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[2] H. J. Bestmann and R. Schmiechen, *Chem. Ber.*, **94**, 751 (1961).

[3] F. Weygand and R. Schmiechen, *ibid.*, **92**, 535 (1959).

[4] For review, see "Neuere Methoden der Präparativen Organischen Chemie," Bd. IV, ed. by W. Foerst, Verlag Chemie, GmbH, Weinheim (1966), p. 200.

[5] *Cf.*, J. A. Meschino and C. H. Bond, *J. Org. Chem.*, **28**, 3129 (1963).

[6] M. L. Wolfrom and H. B. Wood, *J. Amer. Chem. Soc.*, **73**, 2933 (1951); M. L. Wolfrom and K. Anno, *ibid.*, **74**, 5583 (1952).

[7] See, Ref. 4, p. 207.

sodium borohydride (2–12 equivalents) in the presence of boric acid or boric acid and Amberlite IR 120 (H^+)[8] gave unsatisfactory results. Although the formation of L-threose (IV) could only be detected by a weak spot on tlc, predominent formation of by-products was observed in the case of a large excess of the reducing agent and a large amount of II was recovered in the case a slight excess of the hydride. Bis(1,2-dimethylpropyl)borane (disiamylborane) has been used in the reduction of γ-lactones to γ-hydroxyaldehydes.[9] In view of the success of reduction of 2-deoxy-*erythro*-pentono-γ-lactone to 2-deoxy-*erythro*-pentose with the same borane,[10] the reaction of II with an excess of disiamylborane in tetrahydrofuran was performed at room temperature. After borinate ester (III) formed had been hydrolyzed on addition of water, disiamylborinic acid (V) was removed by extraction with ether. L-Threose (IV) was obtained from the aqueous layer as a syrup in a quantitative yield. No crystalline D- or L-threose has so far been obtained, and the crystalline D-threose reported by Freudenberg[11] which showed positive specific rotation appears to be in error.[12] The specific rotation of syrupy L-threose (IV) thus obtained and the melting point of its benzoylhydrazone agreed with the reported values (Table 1). The overall yield of L-threose (IV) from *dextro*-tartaric acid was found to be 46%. The present method seems to be superior to the reported methods in view of the simplicity of procedure and the high yield. The Wohl degradation of L-xylose derivative obtained from sorbitol to give L-threose (IV) requires several steps[16] and the glycol-cleavage of 1,3-benzylidene-L-arabitol derived from L-arabinose affords L-threose (IV) in a lower yield (36% based on L-arabinose).[15,17,18b]

TABLE 1. SPECIFIC ROTATIONS OF IV AND MELTING POINT OF BENZOYLHYDRAZONE OF IV

	Found	Lit. values
$[\alpha]_D$ (in H_2O)	+12.2° (initial)→ +12.6° (after 3 days)	D-form: −12.3°[13] −11°[14] −11.6°[15] L-form: +12.5°[15] +13.1°[16]
Mp of benzoylhydrazone	167.5—169.0°C	L-form: 167—168°C (decomp.)[14]

Reduction of ester chloride (VI) with tri-*n*-butyltin hydride which proved to be an useful reagent in the conversion of acid chloride into aldehyde[19] afforded methyl di-*O*-acetyl-L-threuronate (VII) as a liquid. Although attempts to crystallize VII by means of vacuum distillation or chromatography on silica gel or alumina failed, liquid VII gave crystalline 2,4-dinitrophenylhydrazone in a 38% yield based on VI.

As stated previously, introduction of the acetoxyl group into a position adjacent to the alkoxycarbonyl group facilitates sodium borohydride reduction of the alkoxycarbonyl group to the hydroxymethyl group. Consequently, it was anticipated that 2-deoxy-pentarate ester (X) which could be derived from ester chloride (VI) *via* diazoketone (VIII) by a photochemical rearrangement[3] might afford 2-deoxy-*threo*-pentono-γ-lactone (XI) by a preferential reduction of the methoxycarbonyl group at 5-position. However, the reaction of X (1 mol) with various amounts of sodium borohydride (2.5—5.0 mol) in different solvents (water, methanol, tetrahydrofuran, or 2-propanol) gave unsatisfactory results. Only removal of acetyl groups was observed in the case of methanol solution. Treatment of X in tetrahydrofuran with the hydride resulted in a recovery of X. The reaction product obtained on treatment of X with the hydride in water or 2-propanol gave syrupy material after deacetylation by the ester-exchange reaction followed by hydrolysis of methyl ester groups. The syrup gave a weak spot correspounding to an authentic specimen of XI together with several spots of by-products. Since crystalline diazoketone (VIII), precursor of 2-deoxy-pentarate ester (X), could be scarcely obtained when the reaction of diazomethane with ester chloride (VI) had been carried out according to the reported method,[3] ester chloride (VI) was treated with an excess of diazomethane. The product was subjected to chromatography on silica gel which resulted in the separation of diazoketone (VIII) and another crystalline compound. The structure of epoxide ester (IX) could be assigned to the crystalline compound on the basis of elemental analysis and IR and NMR spectroscopic data. The NMR spectrum of IX in deuteriochloroform exhibited singlets at δ 2.91 (2H) and δ 3.73 (5H) which could be assinged to methylene protons of the epoxide ring, and protons of methyl in the ester and chloromethyl groups, respectively. The NMR spectrum of IX measured in benzene afforded more confirmative evidence, *i.e.*, methylene protons in the epoxide ring exhibited AB quartet [centered at δ 1.84 and 1.92 (J=10.2 Hz)], and protons of the chloromethyl group also split in AB quartet [centered at δ 2.88 and 2.93 (J=12.4 Hz)]. IX also gave a positive test for sodium thiosulfate-phenolphthalein reagent[20] indicating the presence of epoxide ring. The epoxy-ester (IX) may be formed by the reaction of diazoketone (VIII) with

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hydrogen chloride liberated[21] and another mole of diazomethane.[22]

Finally we wish to give some remarks on the optical rotatory properties of some compounds related to aldotetrose. L-Threono-γ-lactone (II) exhibited a negative Cotton effect in the ORD and CD spectra in agreement with the general rule proposed by Okuda, Harigaya, and Kiyomoto.[23] They concluded that the sign of the Cotton effect of aldonolactones is governed by the configuration of carbon atom at 2-position, *i.e.*, (*R*)- and (*S*)-configurations at 2-position gave negative and positive Cotton effects, respectively. The observed negative Cotton effect of L-threono-γ-lactone (II) is consistent with the (*R*)-configuration at 2-position.

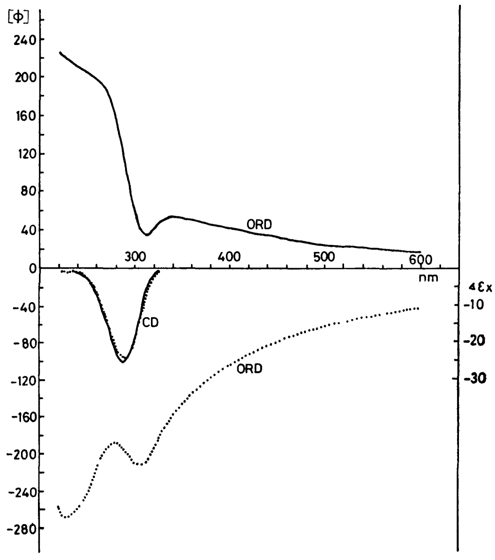

Fig. 1. ORD and CD spectra of L-threose (IV) (——) and D-erythrose (······) in water.

Table 2. ORD and CD spectra of L-threose (IV) and D-erythrose

	ORD in H_2O[a]		CD in H_2O[b]
	$[\phi]_{\min}$	$[\phi]_{\max}$	$\Delta\varepsilon_{\max}$
L-Threose	+ 35° (312 nm)	+188° (268 nm)[c]	−0.024 (288 nm)
D-Erythrose	−213° (304 nm)	−189° (278 nm)	−0.024 (290 nm)

a) L-Threose: after 3 days, measured at 20°C.
D-Erythrose: after 24 hr, measured at 15°C.
b) L-Threose: after 30 hr. D-Erythrose: after a week.
c) Inflection.

An aqueous solution of L-threose (IV) obtained by the disiamylborane reduction of II showed a small negative Cotton effect at *ca.* 290 nm. Cantor and Peniston carried out polarographic studies on aqueous solution of carbohydrates and pointed out the presence of species reducible at dropping mercury cathode and estimated the amount of the reducible form.[24] They considered that the reducible species should be of *aldehydo*-form or its hydrated species of carbohydrates.[24] It was revealed later that the ORD spectra of aqueous solution of aldopentoses and aldohexoses usually exhibit a simple curve in a wavelength region longer than 210 nm and no Cotton effect can be observed in the region of $n \rightarrow \pi^*$ transition of carbonyl of aldehyde group.[25] In spite of the high content of the reducible form,[24] D-ribose also showed no Cotton effect in the region of carbonyl $n \rightarrow \pi^*$ transition. Thus, complete hydration of the free aldehyde group in open chain form of aldopentose or aldohexose was concluded.[26] L-Threose (IV) obtained by acid hydrolysis of an authentic 2,4-*O*-benzylidene-L-threose[18b] also showed a negative Cotton effect at *ca.* 290 nm. This indicates that the negative Cotton effect observed in L-threose (IV) derived from II can not be ascribed to the presence of any carbonyl containing impurity, but is an inherent property of IV (Fig. 1 and Table 2). The signal at δ 9.44 (singlet) in the NMR spectrum of L-threose (IV) in deuterium oxide can presumably be attributed to the proton of the free aldehyde group. Recently, the presence of a weak Cotton effect in the CD spectrum of D-erythrose in water was briefly reported.[27] This was confirmed by the present authors employing a syrupy D-erythrose obtained by the hydrolysis of crystalline 2,4-*O*-ethylidene-D-erythrose[18a] (Fig. 1 and Table 2). *glycero*-Tetrulose appears to be the most probable impurity of these aldotetroses. Rearrangement of L-threose or D-erythrose should result in L- or D-*glycero*-tetrulose, respectively. However, studies on *glycero*-tetrulose revealed that the L-isomer exhibits a positive and the D-isomer a negative Cotton effect in their ORD spectra.[28] Consequently, the negative Cotton effect of L-threose can not be attributed to the presence of L-*glycero*-tetrulose as an impurity. 2,4-*O*-Ethylidene-D-erythrose, starting material for the preparation of D-erythrose, shows a weak negative Cotton effect ($\Delta\varepsilon-$ 0.021) at 293 nm in water. Therefore, we can not hold the presence of a small amount of 2,4-*O*-ethylidene-D-erythrose as an impurity to be responsible for most of the observed negative Cotton effect of D-erythrose.

Tetrose may contain more of the open chain form than pentose and hexose in the ring-chain equilibrium, because furanose, the cyclic form of aldotetrose, is known to be less stable than pyranose. The observed Cotton effect in the region of $n \rightarrow \pi^*$ transition of the carbonyl group seems to indicate that some part of the open chain form of aldotetrose exists in non-hydrated *aldehydo*-form.

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Experimental

The melting points were measured on a Mettler FP2 apparatus and uncorrected. The IR spectra were obtained on a Hitachi EPI-2 Spectrophotometer, the ORD and CD spectra on a Yanagimoto ORD-185, a JASCO ORD/UV-5 and a Roussel-Juan Dichrograph and the NMR spectra on a Varian A-60 or T-60 spectrometer using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard, unless otherwise stated. Commercial silica gel (E. Merck, Darmstadt, Germany, 70—325 mesh) was immersed in 60% aqueous acetic acid and kept standing overnight. The gel was collected by suction filtration and washed thoroughly with water until the filtrate gave neutral test, and dried at 120°C for 15 hr. The silica gel thus treated was used in chromatography.

L-Threono-γ-lactone (II). To an ice-cooled and stirred solution of sodium borohydride (991 mg, 28.3 mmol) in water (15 ml) was added dropwise a solution of half-ester of di-*O*-acetyl-*dextro*-tartaric acid[1] (I, 2.0 g, 8.06 mmol) in water (23 ml). After the mixture had been stirred for 4 hr at room temperature, 2N hydrochloric acid (20 ml) was added and the water was removed under reduced pressure. Methanol was added to the residue and concentrated under reduced pressure. The procedure was repeated 3 times to complete the removal of boric acid as its methyl ester. Extraction of the residue with acetone gave an oily material (1.54 g), which was dissolved in methanol (15 ml) and mixed with potassium hydroxide (2.5 g, 45 mmol) in water (5 ml). The mixture was kept at room temperature for 15 min and then refluxed for 1 hr. 2N Hydrochloric acid (22 ml) was added to the cooled reaction mixture. The residue obtained by evaporating the water *in vacuo* was extracted with ethyl acetate. The oily material (998 mg) obtained from the extract was subjected to a vacuum distillation (0.088 mmHg). The fraction obtained from *ca.* 148°C (bath temp.) crystallized on standing. The crystals were washed with a small amount of ethyl acetate to yield fairly pure II (700 mg, 74%). Recrystallization from the same solvent afforded pure II, mp 67—69°C (lit. values: mp 65—68°C[29]; mp 61—64°C[2]), IR (Nujol mull): 3400 (O–H), 1770 (C=O) cm^{-1}, $[\alpha]_D^{17}=+46.7°$ (c, 1.54, CH_3OH) (lit. values: $[\alpha]_D^{21}=+47.0°$[29]; $[\alpha]_D^{19}=+51.2°$[30]), $[\phi]_{min}=-5210°$ (239.5 nm), $\Delta\varepsilon_{max}=-3.59$ (222.5 nm) (c, 2.11×10^{-3} mol/l, CH_3OH).

Found: C, 40.59; H, 5.14%. Calcd for $C_4H_6O_4$: C, 40.68; H, 5.12%.

Phenylhydrazide. Colorless plates, mp 153—157°C (lit. value: mp 161—161.5°C[29]).

Found: C, 52.98; H, 6.35; N, 12.16%. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38%.

L-Threose (IV). A solution of disiamylborane in tetrahydrofuran was prepared according to the usual method from a solution of 2-methyl-2-butene (4.275 g, 61.1 mmol) in the same solvent (15 ml) and a stock solution of diborane (34.2 ml, 0.445 mmol/ml, 15.2 mmol). To this was added dropwise under ice-cooling a solution of γ-lactone (II, 300 mg, 2.54 mmol) in the same solvent (12 ml) in nitrogen atmosphere. After the mixture had been kept at room temperature for 18 hr, water (1 ml) was added under stirring to the ice-cooled reaction mixture to decompose the excess of disiamylborane. It was then mixed with a further amount of water (60 ml) and stirred for 30 min at room temperature to hydrolyze borinate ester (III). The mixture was extracted with ether (25 ml × 3) to remove disiamylborinic acid (V). The ethereal extract was washed with water (25 ml). The combined aqueous layer and washing were concentrated under reduced pressure. The residue was mixed with methanol and the solvent was removed *in vacuo.* After the procedure had been repeated 3 times, the residue was dried in an evacuated desiccator containing phosphorus pentoxide to give an almost colorless syrup (325 mg, $[\alpha]_D^{20}=+12.2°$ (initial)→ $+12.6°$ (after 3 days) (c, 2.55, H_2O)). The syrup was converted into crystalline benzoylhydrazone according to the reported method.[14] Syrupy L-threose (IV, 48 mg) gave 60 mg (63%) of benzoylhydrazone. Recrystallization from ethanol gave pure hydrazone as colorless fine needles, mp 167.5—169.0°C. IR (Nujol mull): 3500, 3360, 3240 (O–H, N–H); 1647 (amide-I): 1551 (amide-II) cm^{-1}.

Found: C, 55.44; H, 6.01; N, 11.74%. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76%.

Methyl Di-O-acetyl-L-threuronate (VII). A solution of acid chloride (VI,[3] 2.30 g, 8.63 mmol) in tetrahydrofuran (16 ml) was added to tri-*n*-butyltin hydride[31] (2.64 g, 9.07 mmol) over a period of 15 min. After stirring for 100 min, the solvent was removed under reduced pressure. The residue was mixed with petroleum benzine and water and the aqueous layer was washed twice with petroleum benzine. The combined benzine solution was washed with water. The combined aqueous layer was concentrated under reduced pressure to *ca.* 50 ml. The concentrated solution was treated with active charcoal–celite (1:1) and the filtrate was evaporated under reduced pressure. The residue was dried in an evacuated desiccator over phosphorus pentoxide to afford almost colorless syrup (1.57 g). A mixture of the syrup (116 mg), 2,4-dinitrophenylhydrazine (98 mg) and ethanol (3 ml) was refluxed for 3 hr. The crude crystals deposited were dissolved in benzene and the solution was passed through a short column of alumina. The crystals (99 mg, 38% based on acid chloride (VI)) were recrystallized from ethanol to give an analytical specimen, aggregate of yellow needles, mp 146.5—148.0°C (lit. value:[1] 148°C).

Found: C, 43.83; H, 3.94; N, 13.73%. Calcd for $C_{15}H_{16}N_4O_{10}$: C, 43.69; H, 3.91; N, 13.59%.

Methyl L-threo-*2,3-Di-O-acetyl-5-chloro-5-deoxy-4-C-hydroxymethyl-4,4′-anhydro-pentonate (IX).* Acid chloride (VI,[3] 0.0353 mol) was treated with diazomethane (0.107 mol) according to the reported method.[3] Crystalline diazoketone (VIII) obtained by evaporating the solvent under reduced pressure was filtered. Syrupy filtrate was dissolved in benzene–ethyl acetate (8: 2) and chromatographed on silica gel. Epoxy compound (IX) obtained from early fractions crystallized immediately (mp 63—79°C). Farther elution with the same mixed solvent afforded an additional diazoketone (VIII). Change of melting point of IX could not be observed after recrystallization from diisopropyl ether, ethyl acetate, or ether–petroleum benzine. IX gave immediate red coloration for cold sodium thiosulfate-phenolphthalein reagent[20] indicating the presence of the epoxide ring.

Found: C, 45.05; H, 5.08; Cl, 11.95%. Calcd for $C_{11}H_{15}O_7Cl$: C, 44.83; H, 5.13; Cl, 12.03%.

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