

THE TOTAL SYNTHESIS OF 2-DEOXY-DL- AND L-RIBOSES

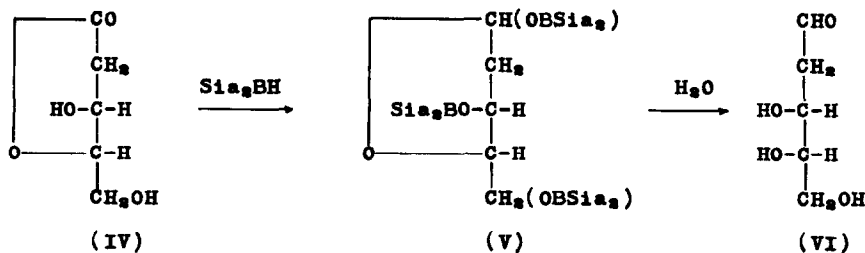
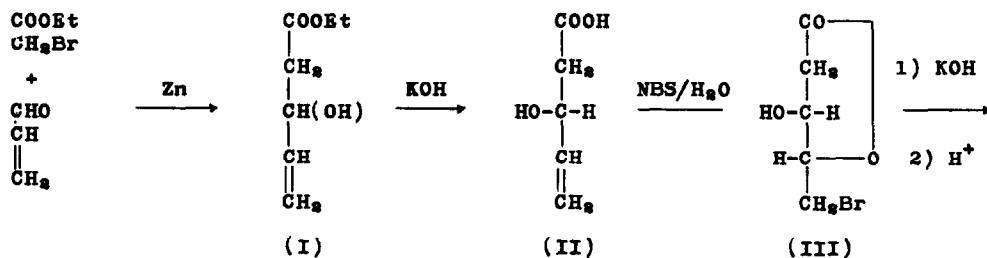
Gen Nakaminami, Masazumi Nakagawa, (late) Sachiko Shioi, Yoko Sugiyama,  
Satoko Isemura and Mikio Shibuya

Department of Chemistry, Faculty of Science, Osaka University,

Toyonaka, Osaka, Japan

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We report herein the total syntheses of 2-deoxy-DL- and L-ribose. As illustrated in the following scheme, the Reformatsky reaction of ethyl bromoacetate with acrolein afforded the  $\beta$ -hydroxy ester (I) in a yield of 40-50%, which was hydrolysed by means of aqueous potassium hydroxide to give the DL-acid (II, 85% yield). The hydroxy acid (II) in an aqueous solution was treated with N-bromosuccinimide and the reaction mixture was extracted with ether yielding the crude bromolactone (III, 43% yield) as a light brown syrup. An analytical sample was obtained by a chromatography on neutral alumina (Woelm, activity III). The  $\gamma$ -lactone structure of III was confirmed by the IR spectrum ( $\gamma$ -lactone :



$\text{>C=O}$ ,  $1775 \text{ cm}^{-1}$ ) and the three-configuration was tentatively assigned on the basis of the studies of the optically active compounds as will be stated later. The DL-bromolactone (III) was treated with aqueous 1N potassium hydroxide at room temperature and the potassium ion was removed by Amberlite IR 120 (H). The acidity of the reaction mixture was adjusted to pH 1, and left to stand for 24 hours, then treated with Dowex 3 (OH) to remove the bromide ion, and finally evaporated under reduced pressure to give 2-deoxy-LL-ribonolactone (IV) as a faintly yellow syrup. The product was found to be highly pure and homogeneous as judged by paper and thin-layer chromatographies. The reduction of DL-IV was attained by disiamylborane (bis-3-methyl-2-butylborane) first reported by H. C. Brown<sup>1</sup>). A solution of DL-IV in anhydrous tetrahydrofuran was mixed with a large excess of the reagent in the same solvent and left to stand at room temperature for 21 hours under nitrogen. The tris-disiamylborinate ester (V) formed was hydrolyzed yielding 2-deoxy-DL-ribose (VI) and disiamylborinic acid. The reaction mixture was extracted with ether to remove the borinic acid, and the aqueous solution was concentrated to an almost colorless syrup, which gave the crystalline anilide of VI on treatment with aniline (61% yield based on IV). The IR spectrum of the DL-anilide was found to be almost superimposable with that of D-anilide. On treatment with benzaldehyde, the DL-anilide gave 2-deoxy-DL-ribose (VI) as colorless syrup (88% yield), which crystallized completely on seeding with the crystals of an authentic D-isomer. The thin-layer chromatography of the product, a mixture of the product with the D-isomer and the D-isomer alone produced one spot, respectively, at the same  $R_f$ -value.

The physical properties of the above-mentioned compounds and their derivatives are tabulated in Table I.

The racemic hydroxy acid (II) in water was treated with a half equivalent of quinine and the salt formed was decomposed yielding (-)-II. The crude (-)-acid (II) was used without further purification to the subsequent reactions. The reaction conditions and procedures which were established in the case of the racemic compounds were adapted to (-)-II. The physical properties of the optically active compounds are summarized in Table II. The specific rotations of 2-deoxy-L-ribose (L-VI) and its anilide thus obtained exceedingly agreed with

TABLE I  
Physical Properties of the Racemic Compounds

Compound	Properties
I	b.p. 63-64°C/2mm ; $n_D^{25}$ 1.4393
anilide from I	m.p. 127.5-128.5°C
II	b.p. 95°C/1mm ; $n_D^{20}$ 1.4630
III	$n_D^{20}$ 1.5214
phenylhydrazide from III	m.p. 137-138°C (decom.)
IV*	$n_D^{20}$ 1.4900
phenylhydrazide from IV	m.p. 134-135°C and 140-142°C (dimorphism)
VI	m.p. 85-91°C
anilide from VI	m.p. 158-159°C (decom.), lit. value <sup>e</sup> ) m.p. 154-155°C

All compounds gave satisfactory IR spectroscopic and elemental analytical data. The asterisk indicates the unpurified substance which lacks the elemental analytical data.

the reported values. Also, the IR spectrum of the L-anilide and the thin-layer chromatogram of L-VI were found to be identical with those of the authentic D-isomer.

The positive specific rotation of the bromolactone ((+)-III) was decreased on hydrolysis of the lactone ring by addition of sodium hydroxide solution suggesting that the lactone ring situates at the right hand in the Fischer projection. The reaction sequence which leads (+)-III to 2-deoxy-L-ribose (L-VI) via 2-deoxy-L-ribonolactone (L-IV) establishes the configuration of the hydroxyl group at C(3) in (+)-III (left side in the Fischer projection). The assignment of the configuration of C(3) was also supported by the ORD measurements of III and IV. Both compounds exhibit positive Cotton effects (III,  $[M]_{\max} = +2940^\circ$  (220m $\mu$ ),  $[M]_{\min} = +2820^\circ$  (213m $\mu$ ). IV,  $[M]_{\max} = +1370^\circ$  (222m $\mu$ ),  $[M]_{\min} = -1480^\circ$  (199m $\mu$ )) caused by  $n \rightarrow \pi^*$  transitions of the lactones, suggesting the same (R)-configuration at C(3)<sup>6</sup>). The mechanistic consideration of the reactions leading from III to IV, i.e., epoxide formation at C(4) and C(5), and the preferential ring opening at C(4) with complete inversion of configuration, is

TABLE II  
Physical Properties of the Optically Active Compounds

Compound	Properties
(R)-(-)-II*	$[\alpha]_D^{25} -9.8^\circ$ (H <sub>2</sub> O, c=0.805)
D-(+)-III	$[\alpha]_D^{25} +52^\circ$ (after 4 days) $\rightarrow$ $+50^\circ$ (after 2 weeks) (H <sub>2</sub> O, c=0.0805), $n_D^{25}$ 1.5207
phenylhydrazide from D-III	m.p. 132-133°C (decom.)
L-(-)-IV*	$[\alpha]_D^{15} -9.5^\circ$ (initial) $\rightarrow$ $-9.8^\circ$ (after 2 weeks) (H <sub>2</sub> O, c=1.08), $n_D^{20}$ 1.4870. lit. value <sup>3</sup> ) $[\alpha]_D^{20}$ $-13.8^\circ$ (initial) $\rightarrow$ $-14.5^\circ$ (after 8.3 days)(H <sub>2</sub> O), $n_D^{20}$ 1.4834
phenylhydrazide from L-IV	m.p. 146-146.5°C and 122-123°C (dimorphism). lit. value <sup>3</sup> ) m.p. 145-146°C
L-VI	m.p. 70-73°C, $[\alpha]_D^{15} +60^\circ$ (at equilibrium)(H <sub>2</sub> O, c=1.06). lit. value <sup>3</sup> ) m.p. 92-95°C, $[\alpha]_D^{16.5} +59^\circ$ (at equilibrium)(H <sub>2</sub> O, c=1.14)
anilide from L-VI	m.p. 174-176°C (decom.), $[\alpha]_D^{14} -55^\circ$ (at equili- brium)(pyridine, c=1.28). lit. value <sup>4</sup> ) m.p. 174- 175°C, $[\alpha]_D -58^\circ$ (after 4 hrs.)(pyridine, c= 1.0)

All compounds gave satisfactory IR spectroscopic and elemental analytical data. The asterisks indicate the unpurified substances which lack the elemental analytical data.

also consistent with the above-mentioned assignment.

The studies on the total synthesis of 2-deoxy-D-ribose (D-VI) starting from (S)-(+)-II are now in progress.

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