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# SYNTHESIS OF FOUR STEREOISOMERS OF 4-AMINO-2-(HYDROXYMETHYL)TETRAHYDROFURAN-4-CARBOXYLIC ACID

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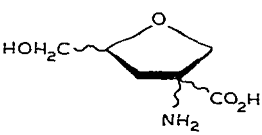
## ABSTRACT

The 5-benzyl ether, **15**, of a 1,2,4,5-pentanetetrol of known 2*S* configuration was made by a multistep synthesis from D-ribose. Ring-closure of the 1-*O*-tosyl derivative, **17**, with retention of configuration, followed by oxidation, gave the 2*S* enantiomer, **22**, of 2-benzyloxymethyl-4-oxotetrahydrofuran. The latter was converted by a hydantion synthesis into the 4-amino-4-carboxylic acid (mixture of 2*S*,4*R* and 2*S*,4*S* isomers, **28** and **29**). Spontaneous lactonization of the 2*S*,4*R* diastereomer proved it to have the "cis" configuration. The remaining, 2*S*,4*S* diastereomer then must be "trans"; it is identical with a natural compound recently isolated from an acid hydrolyzate of diabetic urine. In a parallel synthesis, the 4-*O*-mesyl derivative (de-*O*-isopropylidenated **19**) was cyclized, with inversion at ring-position 2, leading after oxidation to the 2*R* enantiomer, **25**, of the 4-oxotetrahydrofuran. The hydantoin synthesis this time yielded a mixture of the 2*R*,4*R* and 2*R*,4*S* amino-acids. Spontaneous lactonization of the latter showed it to have the "cis" configuration. Absolute configurations were assigned to the four optically active products, based on the known absolute configuration of D-ribose and the known mechanisms of the synthetic reactions.

## INTRODUCTION

An optically active 4-amino-2-(hydroxymethyl)tetrahydrofuran-4-carboxylic acid (**1**) was isolated first in 1974 by Mizuhara *et al.*[1] from an acid hydrolyzate of diabetic urine, and its gross structure was determined by $^{1}$H- and $^{13}$C-n.m.r. data[2]. Although interest in the physiological meaning of this unique amino acid (**1**) flagged slightly after the finding that it was also formed from D-hexoses and urea under the conditions used for acid hydrolysis[3] (indicating **1** to be an artifact*), a different question concerning the path of its formation nevertheless arose. In the present paper, all four possible stereoisomers of **1** were synthesized from D-ribose and D-glucose, and the configuration of **1** isolated from the urine was determined to be (2*S*,4*S*), as briefly reported earlier[4].

*The formation of **1** was independently confirmed by us.



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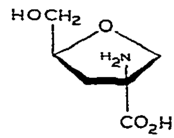
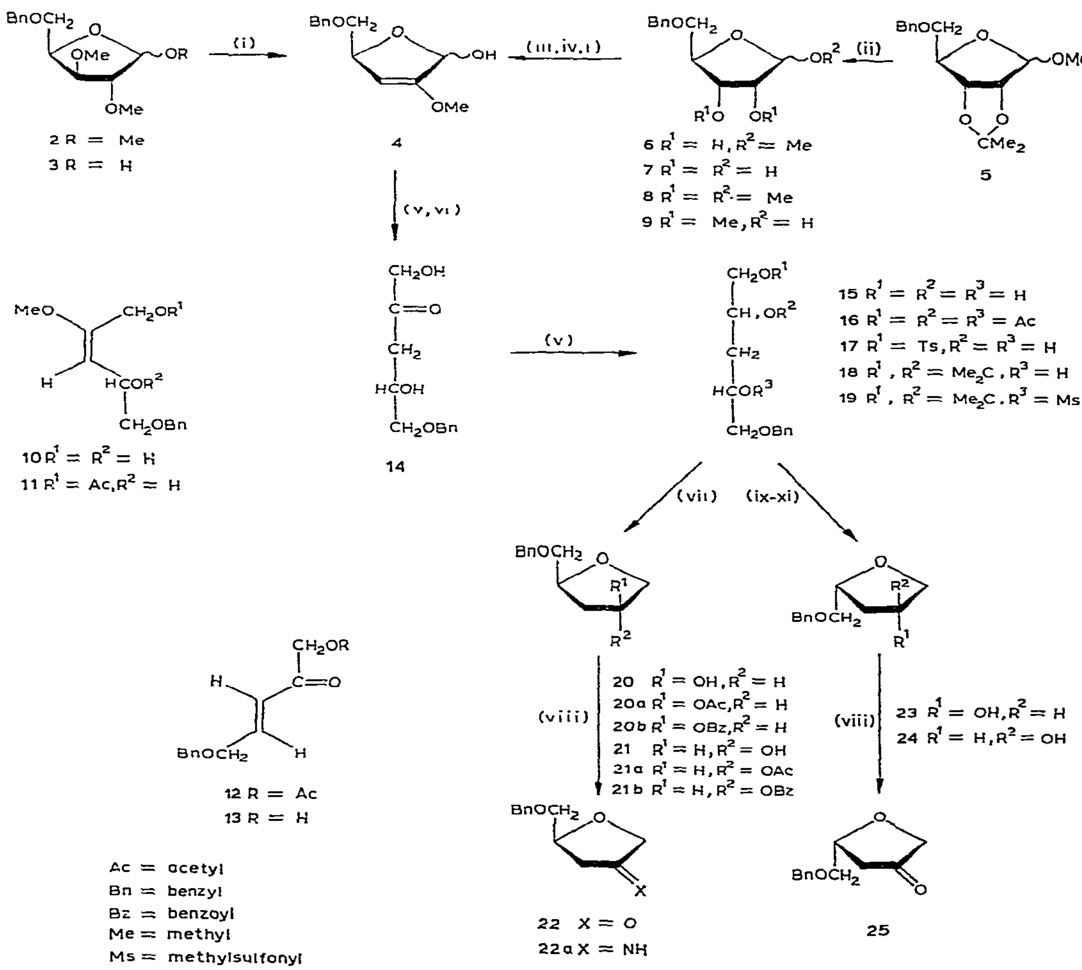


(2S,4S)-1



Ac = acetyl
Bn = benzyl
Bz = benzoyl
Me = methyl
Ms = methylsulfonyl
Ts = tolylsulfonyl

(i) $Ca(OH)_2 \cdot H_2O$ (ii) 0.7% HCl, 100°, 2 h (iii) NaH, MeI (iv) 0.05 M $H_2SO_4$

(v) $NaBH_4$ (vi) Cationic resin (CG-50) (vii) TsCl, $C_5H_5N$, $Et_3N$

(viii) $Me_2SO-Ac_2O$ (ix) $Me_2CO$, $CuSO_4$ (x) MsCl, $C_5H_5N$ (xi) 90% $CF_3CO_2H$, $CH_3ONa$

Scheme I

## RESULTS AND DISCUSSION

From the few synthetic methods generally used for α-alkyl-α-amino acids, the modified Bucherer–Bergs reaction[5] was chosen and applied to the (2*S*)- and (2*R*)-hydroxymethyl-4-oxotetrahydrofuran derivatives **22** and **25**. This method was used successfully for preparing the corresponding amino acid derivative of a pentofuranos-3-ulose[6]. The two enantiomers (**22** and **25**) were to be prepared by changing the cyclization method appropriately *via* a common acyclic intermediate such as **14** or **15**, which may be obtained from 5-*O*-benzyl-3-deoxy-2-*O*-methyl-D-*glycero*-pent-2-enofuranose (**4**). Compound **4** was prepared by two different routes from D-glucose and D-ribose, respectively.

In the first route, methyl 5-*O*-benzyl-2,3-di-*O*-methyl-D-xylofuranoside (**2**) was prepared as an anomeric mixture from D-glucose in 8 steps by the method of Kovác and Petriková[7]. Acid hydrolysis of **2** with 0.05M sulfuric acid afforded 5-*O*-benzyl-2,3-di-*O*-methyl-D-xylofuranose (**3**) in 90% yield. Alkaline β-elimination of **3** with calcium hydroxide[8] gave the 2-enofuranose derivative **4** in 73% yield. The structure of **4** was ascertained from its i.r. absorption at 1670 $cm^{-1}$ and n.m.r. signals at δ 5.53 and 5.77 (enol-ether alkenic protons of the α and β anomers), and further by chemical conversion.

The second, and shorter, route started with simultaneous isopropylidenation and glycosidation of D-ribose[9] followed by benzylation with sodium hydride and benzyl chloride in *N*,*N*-dimethylformamide (DMF) to give methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribofuranoside (**5**) in good yield. The ratio of α to β anomers was ~1:7. Acid hydrolysis of **5** in 0.7% aqueous hydrochloric acid for 2 h at 100° gave the de-*O*-isopropylidenated derivative **6** in 86% yield, together with a small amount of 5-*O*-benzyl-D-ribose (**7**), which was reconverted into **6** by treatment with 0.2% methanolic sulfuric acid. Conventional methylation of **6** with sodium hydride and methyl iodide afforded the corresponding 2,3-di-*O*-methyl derivative (**8**) in 54% yield, which was then hydrolyzed with 0.05M sulfuric acid under reflux for 5 h to give 5-*O*-benzyl-2,3-di-*O*-methyl-D-ribose (**9**) in 90% yield. The same β-elimination reaction with **9** afforded **4**, also in good yield.

At first, conversion of **4** into a dihydrofuran derivative with retention of the enol ether function was attempted. Reduction of **4** with sodium borohydride gave the corresponding pent-2-enitol derivative (**10**) in quantitative yield. The structure of **10** was confirmed by the disappearance of anomeric proton resonances from its n.m.r. spectrum and by i.r. absorption at 1670 $cm^{-1}$. Acetylation of **10** with acetic anhydride in pyridine unexpectedly afforded a mixture of the 1-*O*-acetyl derivative **11** and (*E*)-1-acetoxy-5-benzyloxy-3-penten-2-one (**12**), indicating that isomerization to the keto form followed by β-elimination may readily occur by action of the acetic acid formed. Although formation of the partially acetylated compound **11** was not explained, the structure of **11** was deduced by its i.r. absorption at 1740 $cm^{-1}$ (acetyl) and 1670 $cm^{-1}$ as well as by the intensity of the acetyl signal and the downfield shift of methylene protons at C-1 in the n.m.r. spectrum. The structure of **12** was indicated by the i.r. absorption at 1740 $cm^{-1}$ (acetyl), and 1690 and 1640 $cm^{-1}$ ($\alpha,\beta$-unsaturated ketone), as well as by the large coupling-constant (16 Hz) between two alkenic protons. For intramolecular cyclization, selective 1-*O*-tosylation of **10** with *p*-toluenesulfonyl chloride in pyridine was performed, but the attempt failed because of rapid conversion of **10** into 5-*O*-benzyl-3-deoxy-D-*glycero*-2-pentulose (**14**), followed by further complex reactions, including tosylation–cyclization as mentioned later, $\beta$-elimination, and other reactions. Compound **14** was also obtained directly from **4** in 45% yield by reduction with sodium borohydride followed by treatment with weakly acidic ion-exchange resin; the 3-penten-2-one derivative **13** was also formed ($\sim$10% yield). The structure of **14** could be ascertained by its i.r. absorption at 1720 $cm^{-1}$ and from C-3-methylene signals at $\delta$ 2.45 and 2.68 in the n.m.r. spectrum. Selective 1-*O*-tosylation again, and direct eliminative cyclization of **14** by elevation of temperature, or by action of orthophosphoric acid, failed because of the instability of **14**. It became clear that cyclization of the acyclic compound having an enol ether or carbonyl function held little promise.

Next the cyclization was performed after initial high-yielding reduction of **14** to give an epimeric mixture of 3-deoxypentitol derivatives (**15**), characterized as the corresponding 1,2,4-triacetate **16**. Selective 1-*O*-tosylation of **15** with *p*-toluenesulfonyl chloride in pyridine at $-15°$, followed by addition of triethylamine, gave cyclized compounds (**20** and **21**), which were separated by preparative t.l.c. in 22 and 18% yield, respectively. In this cyclization reaction, complete formation of **20** took 3 days after the addition of triethylamine, whereas **21** was formed rapidly. The intermediate 1-*O*-tosylated mixture (**17**) was observed in t.l.c., but its isolation in pure state could not be achieved, presumably because of its ready conversion into **20** and **21**.

The structures of these tetrahydrofuran derivatives were deduced by n.m.r. spectroscopy. Spectral data for **20** and **21**, together with those of their 4-acetates (**20a** and **21a**) and 4-benzoates (**20b** and **21b**), may be well explained by supposing that **20** and **21** exist predominantly in ${}^{0}E$ and ${}^{3}T_4$ conformations, respectively, as shown in Table I. The structural assignment was also supported by the observed difference in rate of cyclization. The transition state to **20** is considered to be less favorable than that to **21** because of the large non-bonded interaction between *cis*-oriented substituents at C-4 and C-2. The mixture of **20** and **21** was then oxidized with dimethyl sulfoxide–trifluoroacetic anhydride[13] to give the 4-oxo derivative, **22** in 86% yield. This compound exists mainly in the ${}^{0}E$ conformation, as judged from the values of $J_{2,3}$ and $J_{2,3'}$ as shown in Table II.

The enantiomer (**25**) of **22** was also prepared from the epimeric mixture of pentitols **15** in the following manner. Treatment of **15** with acetone and anhydrous cupric sulfate afforded the 1,2-*O*-isopropylidene derivative (**18**) in 81% yield, and its 4-*O*-mesyl derivative mixture (**19**) was then obtained in quantitative yield. De-*O*-isopropylidenation of **19**, followed by cyclization with sodium methoxide caused inversion at C-4 to give a mixture of **23** and **24**, which was then converted into **25** in the manner already described. Comparison of the specific rotations with those of

TABLE I

OBSERVED COUPLING CONSTANTS OF **20**, **21**, AND THEIR ACYL DERIVATIVES, AND CALCULATED VALUES FOR SOME POSSIBLE CONFORMERS

| | *Observed* | | | *Calc.*[a] | | | *Observed* | | | *Calc.*[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **20** | **20a** | **20b** | $^3T_4$ | °E | $^3E$ | **21** | **21a** | **21b** | $^3T_4$ | °E | $^3E$ |
| $J_{2,3}$ | 3.3 | 6.6 | 6.0 | 8.8–11.0 | 7.7–10.0 | 9.2–11.5 | | | ~8.5 | 8.8–11.0 | 7.7–10.0 | 9.2–11.0 |
| $J_{2,3'}$ | 5.0 | 7.4 | 7.8 | 3.1–5.4 | 5.2–7.5 | 1.8–4.0 | | | 6.3 | 3.1–5.4 | 5.2–7.5 | 1.8–4.0 |
| $J_{3,4}$ | 1.5 | 2.7 | 2.5 | 9.2–11.5 | 2.1–4.3 | 9.2–11.5 | | ~4.5 | ~6.0 | 1.8–4.0 | 8.2–11.5 | 1.8–4.0 |
| $J_{3',4}$ | 9.1 | 7.4 | 6.9 | 1.8–4.0 | 8.2–11.5 | 1.8–4.0 | | ~2.0 | 2.2 | 1.8–4.0 | 1.8–4.0 | 1.8–4.0 |
| $J_{4,5}$ | 1.4 | 1.5 | <2.0 | 8.8–11.0 | 0.2–1.4 | 7.7–10.0 | 4.2 | 4.5 | 4.5 | 3.1–5.4 | 5.2–7.5 | 5.2–7.5 |
| $J_{4,5'}$ | 2.9 | 4.2 | 4.2 | 3.1–5.4 | 5.2–7.5 | 5.2–7.5 | 1.7 | 1.8 | 2.0 | 0.6–2.2 | 7.7–10.0 | 0.2–1.4 |

| *Com-pounds* | *Chemical shifts* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *H-2* | *H-3* | *H-3'* | *H-4* | *H-5* | *H-5'* | *H-2'a* | *H-2'b* | *OCH₂Ph* | *OAc* |
| **20** | ~2.25m | 1.88dq | 2.27dq | ~2.25m | 3.94q | 3.67q | 3.56q[b] | 3.71q[b] | 4.53, 4.70ABq | |
| **20a** | 4.19m | 1.82dq | 2.39quint | 5.27dq | 4.01q | 3.82q | ~3.6d[c] (2H) | | 4.61s | 2.02s |
| **20b** | ~4.2m | 2.00m | 2.51quint | 5.55dq | 4.18q | 3.98q | 3.60q[d] | 3.70q[e] | 4.62s | |
| **21** | ~4.5m | ← ~1.95m (2H) → | | ~4.35m | 4.00q | 3.76q | 3.48q | 3.58q | 4.58s | |
| **21a** | 4.31m | ← ~2.05m (2H) → | | 5.33m | 4.14q | 3.82q | 3.52q[f] | 3.62q[g] | 4.59s | 2.06s |
| **21b** | 4.50m | 2.14m | 2.28m | 5.60m | 4.28q | 4.01q | 3.58q[h] | 3.68q[i] | 4.62s | |

[a]Lower value by the Karplus equation[10] and higher value by representative modified equations for carbohydrate systems[11,12]. [b]Vicinal coupling constants (Hz): 2.5. [c]5.5. [d]5.0. [e]6.0. [f]5.7. [g]4.1. [h]3.5. [i]5.1.

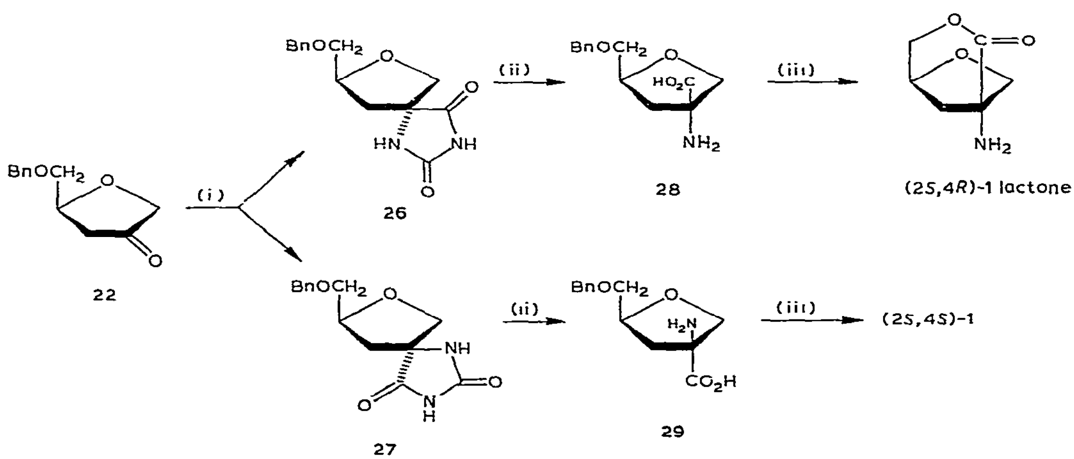
TABLE II

NMR DATA OF **22** AND **26–29**

| *Compounds* | *Chemical shifts (δ)* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *H-2* | *H-3*[a] | *H-3'*[a] | *H-5*[b] | *H-5'*[b] | *H-2'a*[c] | *H-2'b*[c] | *$OCH_2Ph$* | *NH* |
| **22** | 4.49tt | ← 2.46d (2H) → | | 3.86d | 4.10d | 3.57dd | 3.86dd | 4.56s | |
| **26** | 4.38m | 2.67dd | 2.10dd | ← 3.98s (2H) → | | 3.47dd | 3.73dd | 4.58ABq | 6.68, 8.98 |
| **27** | 4.40m | 2.39dd | 2.17dd | 3.87d | 4.15d | ← 3.56d (2H) → | | 4.55s | 6.87, ~7.4 |
| **28**[d] | 4.31m | 2.72dd | 1.94dd | ← 4.02s (2H) → | | 3.66dd | 3.54dd | 4.55s | |
| **29**[d] | 4.38m | 2.42dd | 2.08dd | 4.19d | 3.76d | ← 3.59m (2H) → | | 4.55s | |

| | *Coupling constants (Hz)* | | | | | | |
|---|---|---|---|---|---|---|---|
| | $J_{2,3}$ | $J_{2,3'}$ | $J_{3,3'}$ | $J_{5,5'}$ | $J_{2,2'a}$ | $J_{2,2'b}$ | $J_{2'a,2'b}$ |
| **22** | 7.2 | 7.2 | | 16.8 | 4.5 | 3.5 | 10.3 |
| **26** | 9.3 | 4.0 | 13.4 | | 2.5 | 2.1 | 10.5 |
| **27** | 8.0 | 7.2 | 13.2 | 9.5 | 5.4 | 5.4 | |
| **28** | 9.8 | 6.1 | 13.8 | | 2.9 | 3.5 | 10.2 |
| **29** | 8.2 | 5.4 | 12.4 | 9.4 | | | |

[a,b,c]These pairs of methylene protons could not be assigned. [d]In methanol-$d_4$.




(i) KCN, $(NH_4)_2CO_3$, $CO_2$ 50 atm. (ii) $Ba(OH)_2$, $H_2O$, reflux, 1 day, (iii) $H_2$, Pd–C

Scheme II

the enantiomers indicates that cyclization to the tetrahydrofuran derivatives (**23** and **24**) proceeds exclusively by the SN2 mechanism.

The (2*S*)-4-oxo derivative (**22**) was treated with potassium cyanide and ammonium carbonate in methanol at 50° under 50 atm pressure of carbon dioxide[6] to afford two epimeric hydantoin derivatives (**26** and **27**) in 6:1 ratio and 57% total

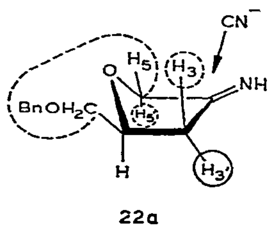
TABLE III

COMPARISON OF PHYSICAL PROPERTIES OF 4-AMINO-2-(HYDROXYMETHYL)TETRAHYDROFURAN-4-CARBOXYLIC ACID AND ITS DERIVATIVES

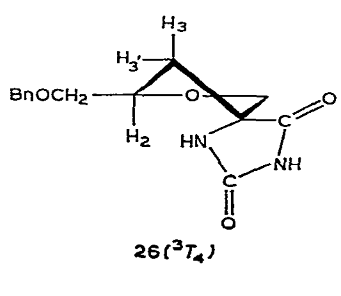
| *Compound* | *M.p. (degrees)* | $[\alpha]_D$ *(solvent) (degrees)* | $\nu_{C=O}$ *(cm$^{-1}$)* | *Retention time (min)*[a] |
|---|---|---|---|---|
| (2*S*,4*S*)-**1** | 250–253 | +35° ($H_2O$) | 1645 | 53.6 |
| (2*R*,4*R*)-**1** | 252–255 | −28° ($H_2O$) | 1650 | 53.6 |
| (2*S*,4*R*)-**1** lactone | 180–185 | +18° (MeOH) | 1735 | [b] |
| (2*R*,4*S*)-**1** lactone | 182–185 | −21° (MeOH) | 1740 | [b] |
| Natural product | 251–255 | +38° ($H_2O$) | 1640 | 53.4 |

[a]Analyzed under the conditions for acidic and neutral amino acids: column (9 × 550 mm) packed with Hitachi custom ion-exchange resin 2613, elution rate 60 mL/h, temperature 55°, buffer 0.20M sodium citrate buffer (pH 3.25) containing 8% ethanol. [b]No peak was observed until 210 min under the analytical conditions for basic amino acids: column (9 × 250 mm) packed with Hitachi custom ion-exchange resin 2615, elution rate 60 mL/h, temperature 60°, buffer 0.35M sodium citrate buffer (pH 5.28) containing 0.57M sodium chloride.

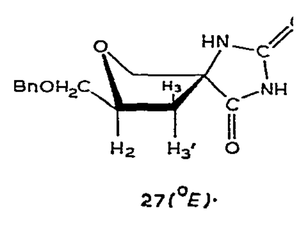
yield. These epimers, separated by preparative t.l.c., showed carbonyl absorption typical of hydantoins at 1740 and 1780 cm$^{-1}$ in the i.r. spectra. The n.m.r. data for **26** and **27** indicated $^3T_4$ and $^0E$ conformations (Table II), respectively, but definitive conclusions on the stereochemistry at the spiro carbon atom could not be drawn. However, the following chemical conversion established their structures. Both epimers were hydrolyzed in barium hydroxide solution under reflux for 1 day to give the corresponding amino acid derivatives (**28** and **29**) in 48 and 54% yields, respectively. Hydrogenolysis of **28** and **29** in methanol in the presence of palladium-on-charcoal and acetic acid gave an aminolactone derivative, (2*S*,4*R*)-**1** lactone, and an amino acid derivative, (2*S*,4*S*)-**1**, both in quantitative yields. The former showed six-membered lactone absorption at 1740 cm$^{-1}$ in the i.r. spectrum. The compound (2*S*,4*S*)-**1** was identical in all respects, with the amino acid isolated from an acid hydrolyzate of diabetic urine as shown in Table III. The stereoselectivity of hydantoin formation constitutes an interesting stereochemical problem, and may be explained by steric factors, as deduced from the behavior of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose[6]. Supposing that the most probable intermediate[6],




22a




26($^3T_4$)

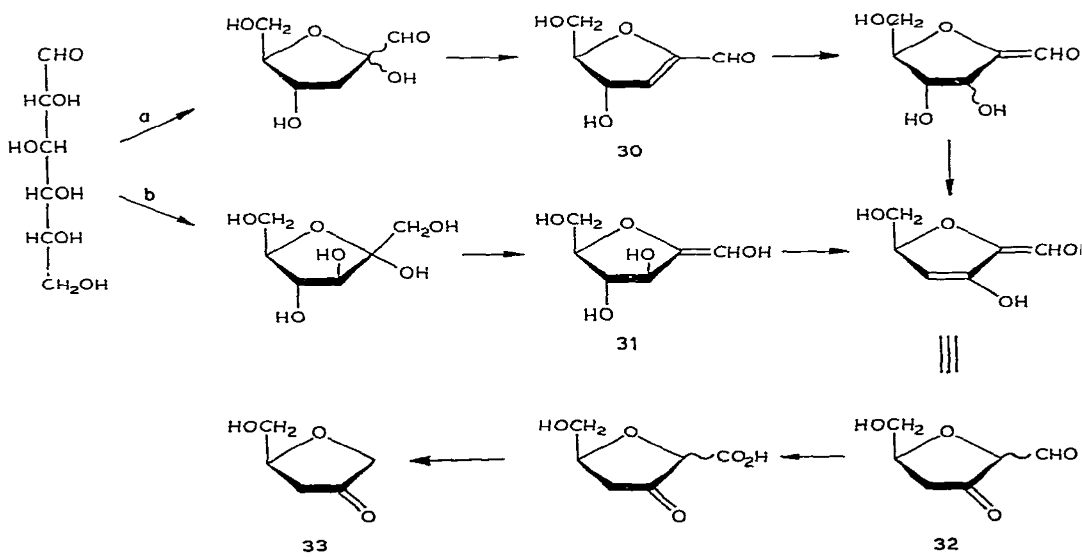



27($^0E$)

namely, the imine derivative (**22a**), adopts the $^{0}E$ conformation like **22**, then steric hindrance caused by the quasi-axial proton (H-5′) seems to be unexpectedly larger than that by the turned-back part of the envelope, including the quasi-equatorial proton (H-5) and benzyloxymethyl group, as shown in the scheme.

The enantiomers of (2*S*,4*R*)-**1** lactone and (2*S*,4*S*)-**1** were synthesized likewise from the (2*R*)-4-oxo derivative **25**. Table III summarizes the specific rotations, melting points, and chromatographic behavior of the four 4-amino-2-(hydroxymethyl)tetrahydrofuran-4-carboxylic acids synthesized [(2*S*,4*S*)-**1**, (2*R*,4*R*)-**1**, (2*S*,4*R*)-**1** lactone, and (2*R*,4*S*)-**1** lactone], and the amino acid isolated from urine. These data, plus the $^{1}$H-n.m.r. spectrum, confirm the identity of (2*S*,4*S*)-**1** with the natural amino acid.

Thus, the configuration at C-2 of the amino acid obtained from the hydrolyzate of hexose and urea was clearly established as *S*. The fact suggests a new type of degradation pathway, different from the well known one for aldoses under acidic conditions to furfural[14]. It seems probable that (2*S*,4*S*)-**1** is formed *via* 2*S*-(hydroxymethyl)-4-oxotetrahydrofuran (**33**). One of the most plausible intermediates to **33** is 2*S*-(hydroxymethyl)-4-oxo-tetrahydrofuran-2-yl aldehyde (**32**), which may arise from D-glucose through path *a* or *b*, as shown in the following scheme *via* intermediate **30** or **31**, both of which have been proposed in the acid degradation of aldoses[14,15].




EXPERIMENTAL

*General methods.* — Melting points were determined with a Mel–Temp melting-point apparatus and are not corrected. Optical rotations were measured by using a 0.5-dm tube with Carl Zeiss LEP-Al or JASCO DIP-4 polarimeter. I.r. spectra were recorded with a Hitachi EPI-G2 grating spectrometer. N.m.r. spectra were recorded at 100 MHz with a JEOL JNM PS-100 spectrometer for solutions in chloroform-*d* (unless otherwise stated) containing tetramethylsilane as the internal standard. Chemical shifts and coupling constants are recorded in $\delta$ and Hz units, and i.r. frequencies in $cm^{-1}$. Column chromatography and preparative t.l.c. were performed on Wakogel C-200 (Wako Pure Chemical Industries, Ltd.) and Kieselgel 60 $HP_{254}$ (Merck), respectively. Evaporations were conducted under diminished pressure at a temperature not exceeding 50°.

*5-O-Benzyl-2,3-di-O-methyl-*D*-xylofuranose* (3). — Methyl 5-*O*-benzyl-2,3-di-*O*-methyl-D-xylofuranoside[7] (37.4 g, 0.133 mol) was hydrolyzed in 0.05M aqueous sulfuric acid (1 L) containing acetone (100 mL) for 3 h at 100°. The mixture was made neutral with basic lead carbonate and undissolved material was filtered off. Evaporation of the filtrate gave **3** (32.1 g, 90%) as a syrup, $[\alpha]_D$ −5.0° (*c* 1, ethanol); $\nu_{max}^{NaCl}$ 3400 (OH) $cm^{-1}$; n.m.r.: 5.40 (d, $J_{1,2}$ 4.5, H-1 of $\alpha$ anomer), and 5.13 (s, H-1 of $\beta$ anomer). The ratio of $\alpha$ to $\beta$ anomer was ~2:1.

*Anal.* Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.31; H, 7.46.

*5-O-Benzyl-3-deoxy-2-O-methyl-*D-glycero*-pent-2-enofuranose* (4). — From **3**. A solution of **3** (13 g, 49 mmol) in 0.02M aqueous calcium hydroxide (1 L) was heated under a stream of nitrogen for 16 h at 50°. The mixture was made neutral with carbon dioxide and insoluble material was filtered off. The filtrate was evaporated to yield **4** (8.5 g, 73%) as a syrup; $\nu_{max}^{NaCl}$ 1670 (C=C) $cm^{-1}$; n.m.r., $\alpha$ anomer: 5.53 (broad s, H-3), 4.68 (d, $J_{1,3}$ 2.0, H-1), 4.83 (sex, $J_{3,4}$ 1.7, $J_{4,5} = J_{4,5'}$ 3.0, H-4), 3.72 (s, OMe), and 4.58 (s, OBn); $\beta$ anomer: 5.78 (d, $J_{3,4}$ 3.8, H-3), 5.06 (m, $J_{4,5} = J_{4,5'}$ = 5.3, H-4), 3.72 (s, OMe), and 4.58 (s, OBn). The ratio of $\alpha$ to $\beta$ anomer was ~2:1.

*Anal.* Calc. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.62; H, 6.77.

From **9**. Alkaline treatment of **9** in the same manner as just described gave **4** in 70% yield.

*Methyl 5-O-benzyl-2,3-O-isopropylidene-*D*-ribofuranoside* (5). — To a chilled solution of methyl 2,3-*O*-isopropylidene-D-ribofuranoside[9] (35 g, 0.17 mol) in DMF (500 mL) were added sodium hydride (11 g, 0.205 mol) and then benzyl chloride (26 mL, 0.22 mol) in several portions with stirring. The mixture was poured into ice–water, and extracted with ether. Evaporation of the extract followed by distillation gave pure **5** (43 g, 88%), b.p. 136°/0.01 mmHg; n.m.r.: 4.92 (s, H-1), 4.65 (d, $J_{2,3}$ 5.4, H-2), 4.52 (d, H-3), 4.37 (q, $J_{4,5}$ 5.6, $J_{4,5'}$ 5.8, H-4), 3.50 (q, $J_{5,5'}$ 10.0, H-5), 3.42 (q, H-5'), 4.60 (ABq, OBn), 1.25 and 1.44 (each s, $Me_2C$).

The ratio of $\alpha$ to $\beta$ anomers was 7:1, and the n.m.r. data given are for the former.

*Anal.* Calc. for $C_{16}H_{22}O_5$: C, 65.31; H, 7.48. Found: C, 64.92; H, 7.41.

*Methyl 5-O-benzyl-2,3-di-O-methyl-*D*-ribofuranoside* (8). — A suspension of **5** (40 g, 0.14 mol) in 0.7% aqueous hydrochloric acid was boiled for 2 h under gentle reflux. The mixture was made neutral and extracted with ether. A syrupy residue obtained by evaporation of the extract was fractionated on a column of silica gel with 4:1 benzene–ethyl acetate as eluant to give **6** (29.7 g, 86%) as a syrup, together with a small amount of 5-*O*-benzyl-D-ribofuranose (**7**, 1.7 g, 5%).

To a stirred, chilled solution of **6** (28 g, 0.11 mol) in DMF (700 mL) was added, portionwise sodium hydride (14.4 g, 0.3 mol) and then methyl iodide (20 mL, 0.325 mol) dropwise. The mixture was poured into ice–water and extracted with ether. A syrupy residue obtained by evaporation of the extract was distilled to give **8** (16.7 g, 54%), b.p. 154–161°/0.05 mmHg, $[\alpha]_D$ −22° (*c* 1, chloroform); n.m.r.: 4.90 (d, $J_{1,2}$ 1.0, H-1), 3.72 (q, $J_{2,3}$ 6.1, H-2), 3.83 (q, $J_{3,4}$ 4.0, H-3), 4.21 (m, H-4), 3.59 (q, $J_{4,5}$ 2.0, $J_{5,5'}$ 9.8, H-5), 3.52 (q, $J_{4,5'}$ 7.2, H-5') 4.58 (s, OBn), 3.47, 3.38 and 3.34 (each s, OMe).

*Anal.* Calc. for $C_{15}H_{22}O_5$: C, 63.83; H, 7.80. Found: C, 63.43; H, 8.02.

*5-O-Benzyl-2,3-di-O-methyl-*D*-ribofuranose* (**9**). — To a solution of **8** (18.7 g, 66 mmol) in acetone (100 mL) was added 1 L of 0.5M sulfuric acid. The mixture was heated for 5 h at 100°, and, after cooling, made neutral with basic lead carbonate. The undissolved mass was filtered off and the filtrate evaporated to give **9** (16.1 g, 90%) as a syrup, $[\alpha]_D$ −17° (*c* 1.4, chloroform); n.m.r.: 5.31 (broad s, H-1), 4.02 (d, $J_{2,3}$ 5.2, H-2), 4.15 (q, $J_{3,4}$ 4.0, H-3), 4.31 (m, H-4), 3.76 (q, $J_{4,5}$ 1.0, $J_{5,5'}$ 10.2, H-5), 3.64 (q, $J_{4,5'}$ 4.4, H-5'), 4.55 (s, OBn), 3.48 and 3.38 (each s, OMe).

*Anal.* Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 63.05; H, 7.92.

(E)*-5-O-Benzyl-3-deoxy-2-O-methyl-*D-glycero*-pent-2-enitol* (**10**). — To a chilled suspension of **4** (8.5 g, 36 mmol) in water (100 mL) was added sodium borohydride (1.6 g, 43 mmol) in portions with stirring. The mixture, which became a clear solution, was adjusted with acetic acid to pH 8.0, and evaporated to dryness. The residue was extracted with chloroform, and evaporation of the extract gave crude **10** (8.5 g) as a syrup. Complete removal of sodium acetate from the product was difficult because of instability to the acid, and an analytically pure sample could not be obtained. It showed $\nu_{max}^{NaCl}$ 1670 (C=C) cm$^{-1}$; n.m.r.: 4.15 (ABq, $J_{AB}$ 12, H-1 and H-1'), 4.55 (s, H-3), 3.45 (d, $J_{4,5} = J_{4,5'}$ 5.0, H-5 and H-5'), and 4.56 (s, OBn).

*Acetylation of* **10**. — Compound **10** (50 mg, 0.2 mmol) was acetylated conventionally with acetic anhydride (400 mg, 3.9 mmol) in pyridine (2 mL). The mixture was separated by preparative t.l.c. with 4:1 benzene–ethyl acetate to give (*E*)-1-*O*-acetyl-5-*O*-benzyl-3-deoxy-2-*O*-methyl-D-*glycero*-pent-2-enitol (**11**, 20 mg) and (*E*)-1-acetoxy-5-benzyloxy-3-pentene-2-one (**12**, 20 mg). Compound **11** had $\nu_{max}^{NaCl}$ 1670 (C=C) and 1740 (ester) cm$^{-1}$; n.m.r.: 4.65 (s, H-1 and H-1'), 3.48 (two q, H-5 and H-5'), 4.58 (s, OBn), and 3.54 (s, OMe); **12**: $\nu_{max}^{NaCl}$ 1690 (C=O), 1640 (C=C), and 1740 (ester) cm$^{-1}$; n.m.r.: 4.82 (s, H-1 and H-1'), 6.24 (dt, $J_{3,4}$ 16, $J_{3,5}$ 2.0, H-3), 6.96 (dt, H-4), 4.20 (q, H-5 and H-5'), 4.36 (s, OBn), and 2.18 (s, OAc).

*5-O-Benzyl-3-deoxy-*D-glycero*-2-pentulose* (**14**). — Compound **4** (2.4 g, 10 mmol) was reduced with sodium borohydride (0.38 g, 10 mmol) in the same manner as described for **10**. The mixture was stirred with an excess of weakly acidic ion-exchange resin (CG-50, $H^+$-form) for 24 h. Evaporation of the filtrate gave a syrup, which was then fractionated on a column of silica gel with 4:1 benzene–ethyl acetate as an eluant to give **14** (1 g, 45%) as a syrup, together with a faster-moving component, (*E*)-1-hydroxy-5-benzyloxy-3-penten-2-one (**13**, 300 mg, 10%). Compound **13**, a syrup had $\nu_{max}^{NaCl}$ 1690 (C=O) and 1640 (C=C) cm$^{-1}$; n.m.r.: 6.46 (dt, $J_{3,4}$ 16.2, H-3), 7.01 (dt, $J_{4,5}$ 3.9, H-4), 4.44 and 4.60 (each s, H-1 and H-1', and OBn). Compound **14** had

$[\alpha]_D$ −9.0° (*c* 1, methanol); $\nu_{max}^{NaCl}$ 1720 (C=O) cm$^{-1}$; n.m.r.: 4.24 (s, H-1), 2.45 (q, $J_{3,4}$ 5.0, $J_{3,3'}$ 16, H-3), 2.68 (q, $J_{3',4}$ 7.5, H-3'), 3.55 (q, $J_{4,5}$ 4.8, $J_{5,5'}$ 9.6, H-5), 3.44 (q, $J_{4,5'}$ 6.0, H-5'), and 4.52 (s, OBn).

*Mixture of 5-O-benzyl-3-deoxy-*D-erythro- *and* -D-threo-*pentitols* (**15**). — Compound **14** (1.2 g, 5.4 mmol) was reduced with sodium borohydride (0.24 g, 6 mmol) as described for **10** to yield crude **15** (1.0 g), which was then characterized as the 1,2,4-triacetate **16**, syrup, $\nu_{max}^{NaCl}$ 1740 (ester) cm$^{-1}$; n.m.r.: 3.54 and 3.56 (two d, $J_{1,2} = J_{1',2}$ 4.5, H-1 of 2 epimers), 4.00 and 4.03 (two q, $J_{4,5}$ 6.0 and 5.7, H-5 of 2 epimers, respectively), 4.27 (q, $J_{4,5'}$ 3.6, H-5'), 5.1 (m, H-2 and H-4), 4.54 (t, OBn), and 2.04 (s, 3 OAc).

*Anal.* Calc. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.29; H, 6.86.

*Mixture of 5-O-benzyl-3-deoxy-1,2-O-isopropylidene-4-O-(methylsulfonyl)*-D-erythro- *and* -D-threo-*pentitols* (**19**). — Compound **15** (2.0 g, 8.9 mmol) was isopropylidenated conventionally with acetone (150 mL) in the presence of anhydrous cupric sulfate (10 g). The product was fractionated on a column of silica gel with 20:1 benzene–methanol as eluant to give **18** (1.9 g, 81%), $[\alpha]_D$ −5.7° (*c* 2, chloroform); $\nu_{max}^{NaCl}$ 1380 (Ms) cm$^{-1}$.

*Anal.* Calc. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.79; H, 8.30.

Compound **18** (1.8 g, 6.8 mmol) was methanesulfonylated to give **19** (1.9 g, 95%), $[\alpha]_D$ −5.0° (*c* 2, chloroform), $\nu_{max}^{NaCl}$ 1360 and 1180 (Ms) cm$^{-1}$; n.m.r.: 1.85–2.10 (m, H-3 and H-3'), 3.5–3.9 (m, H-1, H-5, and H-5'), 4.0–4.3 (m, H-1 and H-2), 4.95 (m, H-4), 1.32 and 1.39 (each s, $Me_2C$), 3.02 and 3.04 (each s, total intensity: 3H), and 4.56 (s, OBn). The ratio of the two C-2 epimers was deduced to be ~2:1 by the intensity of two OMs signals.

*Anal.* Calc. for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02; S, 9.31. Found: C, 56.07; H, 7.32; S, 9.50.

(2S,4S)-*2-Benzyloxymethyl-4-hydroxytetrahydrofurans* (**20**) *and its* (2S,4R)-*isomer* (**21**). — To a chilled solution of **15** (2.4 g, 10.6 mmol) in pyridine (30 mL) was added *p*-toluenesulfonyl chloride (2.42 g, 12.7 mmol) at −15° with stirring. The temperature was maintained until the starting compound disappeared (t.l.c.) and was then raised gradually to room temperature. After addition of triethylamine (2 mL), the mixture was kept for 2 days, poured into dilute hydrochloric acid, and extracted with ether. Evaporation of the extract gave a syrup that was fractionated by preparative t.l.c. on silica gel to give **20** (538 mg, 24%) and **21** (387 mg, 17.5%), respectively.

Compound **20** had: $[\alpha]_D$ +21° (*c* 0.8, chloroform); $\nu_{max}^{NaCl}$ 3400 (OH) cm$^{-1}$; n.m.r. data in Table I.

*Anal.* Calc. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.81; H, 7.73.

Compound **21** had: $[\alpha]_D$ +3.6° (*c* 0.8, chloroform); $\nu_{max}^{NaCl}$ 3400 (OH) cm$^{-1}$; n.m.r. data in Table I.

*Anal.* Calc. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 69.58; H, 7.78.

Conventional acetylation and benzoylation of both isomers gave the corresponding 4-acetates (**20a** and **21a**) and 4-benzoates (**20b** and **21b**), respectively, which were characterized only by n.m.r. spectroscopy, as shown in Table I.

(2S)-*Benzyloxymethyl-4-oxo-tetrahydrofuran* (**22**). — To a chilled mixture of dichloromethane (5 mL) and dimethyl sulfoxide (2.8 g, 36 mmol) was added at $-18°$ with stirring, trifluoroacetic anhydride (3.8 g, 18 mmol), followed by the mixture of **20** and **21** (~3:2) just described in dichloromethane (5 mL). After 30 min, the mixture was made neutral with triethylamine, and extracted with ether after the addition of water. Evaporation of the extract gave a syrup that was purified on a column of silica gel to yield **22** (692 mg, 86%), $[\alpha]_D$ $+19°$ (*c* 0.9, chloroform); $\nu_{max}^{NaCl}$ 1760 (C=O) $cm^{-1}$; n.m.r. data in Table I.

*Anal.* Calc. for $C_{12}H_{14}O_3$: C, 66.65; H, 6.71. Found: C, 67.01; H, 6.78.

(2R,4R)-*2-Benzyloxymethyl-4-hydroxytetrahydrofuran* (**23**), *and its* (2R,4S)-*isomer* (**24**). — A solution of **19** (1.9 g, 6 mmol) in 90% trifluoroacetic acid (5 mL) was kept at room temperature until the starting compound disappeared, and was then evaporated directly to give a syrupy mixture of 5-*O*-benzyl-3-deoxy-4-*O*-mesyl-D-*erythro*- and D-*threo*-pentitols. This mixture (1.1 g, 3.8 mmol) was then dissolved in methanol containing sodium (0.2 g, 8 mmol) and the solution kept for 24 h at room temperature. The solvent was evaporated and the residue was shaken with chloroform–water. Evaporation of the dried chloroform layer gave a syrupy mixture of two components, separated on preparative t.l.c. to yield **23**, $[\alpha]_D$ $-24°$ (*c* 1, chloroform), and **24**, $[\alpha]_D$ $-2.5°$ (*c* 1, chloroform). The i.r. and n.m.r. data were identical with those of **20** and **21**, respectively.

(2R)-*Benzyloxymethyl-4-oxo-tetrahydrofuran* (**25**). — This compound was prepared from a mixture of **23** and **24** as described for **22**; yield 87%, $[\alpha]_D$ $+22°$ (*c* 2, chloroform). The i.r. and n.m.r. data were identical with those of **22**.

*Anal.* Calc. for $C_{12}H_{14}O_3$: C, 66.65; H, 6.71. Found: C, 66.30; H, 6.81.

(2S,4R)-*2-Benzyloxymethyl-4-*C-*(spiro-5-hydantoin)tetrahydrofurans* (**26**) *and its* (2S,4S) *isomer* (**27**). — A mixture of **22** (639 mg, 3.1 mmol), potassium cyanide (1.0 g, 15 mmol), and ammonium carbonate (2.0 g, 21 mmol) in methanol (30 mL) was heated in an atmosphere of carbon dioxide (50 atm) for 24 h at 50°. The solvent was evaporated and the residue extracted with chloroform. Evaporation of the extract gave a crystalline mixture of two products (490 mg), which were separated by preparative t.l.c. to give **26** (388 mg, 45%) and **27** (64 mg, 7.5%), respectively.

Compound **26** had m.p. 134–135°, $[\alpha]_D$ $+5.2°$ (*c* 0.8, methanol); $\nu_{max}^{KBr}$ 1780 and 1740 $cm^{-1}$; n.m.r. data in Table II.

*Anal.* Calc. for $C_{14}H_{16}N_2O_4$: C, 60.87; H, 5.80; N, 10.14. Found: C, 60.51; H, 5.86; N, 10.00.

Compound **27** had m.p. 126–127°, $[\alpha]_D$ $+12.5°$ (*c* 0.5, methanol); $\nu_{max}^{KBr}$ 1780 and 1740 $cm^{-1}$; n.m.r. data in Table II.

*Anal.* Calc. for $C_{14}H_{16}N_2O_4$: C, 60.87; H, 5.80; N, 10.14. Found: C, 60.79; H, 5.95; N, 9.81.

The enantiomers of **26** and **27**, prepared from **25** in the same manner, showed the identical i.r. and n.m.r. spectra, and had specific rotations of $-7.0°$ (*c* 2, methanol) and $-13.5°$ (*c* 1, methanol), respectively.

(2S,4R)-*4-Amino-2-(benzyloxymethyl)tetrahydrofuran-4-carboxylic acid* (**28**). —

A suspension of **26** (93 mg, 0.34 mmol) and barium hydroxide (200 mg, 1.2 mmol) in water (7 mL) was boiled under reflux until the starting material disappeared (t.l.c.), and was then kept for 30 min at 100° after the addition of an excess of ammonium carbonate. The mixture was cooled and the precipitate was filtered off and washed with ethanol. The filtrate and washings were evaporated to give a crystalline residue, which was recrystallized from ethanol–hexane to afford pure **28** (41 mg, 48%), m.p. 192–195°, $[\alpha]_D$ +7.8° (*c* 0.7, methanol); $\nu_{max}^{KBr}$ 1650 (carboxylate) $cm^{-1}$; n.m.r. data in Table II.

*Anal.* Calc. for $C_{13}H_{17}NO_4$: C, 62.40; H, 6.40; N, 5.60. Found: C, 62.30; H, 5.90; N, 5.56.

The enantiomer of **28**, prepared from that of **26** in the same manner, showed the identical i.r. and n.m.r. spectra, and had $[\alpha]_D$ −11° (*c* 0.8, methanol).

(2S,4S)-*4-Amino-2-(benzyloxymethyl)tetrahydrofuran-4-carboxylic acid* (**29**). — Alkaline hydrolysis of **27** (47 mg, 0.17 mmol) with barium hydroxide as described for **28** gave **29** (23 mg, 54%), m.p. 186–189°, $[\alpha]_D$ +18° (*c* 0.8, methanol); n.m.r. data in Table II.

*Anal.* Calc. for $C_{13}H_{17}NO_4$: C, 62.40; H, 6.40; N, 5.60. Found: C, 62.68; H, 6.36; N, 5.62.

The enantiomer of **29** prepared from that of **27** in the same manner showed the identical i.r. and n.m.r. spectra, and had $[\alpha]_D$ −21° (*c* 0.5, methanol).

(2S,4R)-*4-Amino-2-(hydroxymethyl)tetrahydrofuran-4-carboxylic acid 4′,2′-lactone* [(2S,4R)-**1** *lactone*]. — Compound **28** (18 mg, 0.07 mmol) was hydrogenolyzed in the presence of palladium-on-charcoal and acetic acid (1 mL) in methanol (25 mL) and then processed to give a stiff syrup (11 mg, 72%), which crystallized from water–ethanol–ether to give the title compound having the physical constants given in Table III, n.m.r.: 4.75 (m, H-2), 4.55 (broad s, H-5 and H-5′), 4.27 and 4.12 (each d, H-2′a and H-2′b).

*Anal.* Calc. for $C_6H_9NO_3$: C, 50.34; H, 6.29; N, 9.79. Found: C, 49.98; H, 6.02; N, 10.13.

The enantiomer of the title compound, namely (2*R*,4*S*)-**1** prepared from that of **28**, showed identical i.r. and n.m.r. spectra, and some of its physical properties are given in Table III.

(2S,4S)-*4-Amino-2-(hydroxymethyl)tetrahydrofuran-4-carboxylic acid* [(2S,4S)-**1**]. — Compound **29** (13 mg, 0.05 mmol) was hydrogenolyzed as described for (2*S*,4*R*)-**1** lactone to give the title compound as crystals (6 mg, 71%) having physical constants given in Table III; n.m.r. 4.85 (m, H-2), 2.84 (d, $J_{2,3} = J_{2,3'}$ 7.5, H-3 and H-3′), 4.45 and 4.64 (each d, $J_{5,5'}$ 11.0, H-5 and H-5′), and 4.14 (d, $J_{2,2'a} = J_{2,2'b}$ 5.0, H-2′a and H-2′b).

*Anal.* Calc. for $C_6H_{11}NO_4$: C, 44.72; H, 6.83; N, 8.70. Found: C, 45.81; H, 6.91; N, 8.23.

The enantiomer of the title compound, namely (2*R*,4*R*)-**1**, prepared from that of **29**, showed identical i.r. and n.m.r. spectra, and some of its physical properties are given in Table III.

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