ABSOLUTE CONFIGURATION OF 4-AMINO-3-HYDROXY-6-METHYLHEPTANOIC ACID PRESENT IN PEPSTATIN A AND STEREOSPECIFIC SYNTHESIS OF ALL FOUR ISOMERS

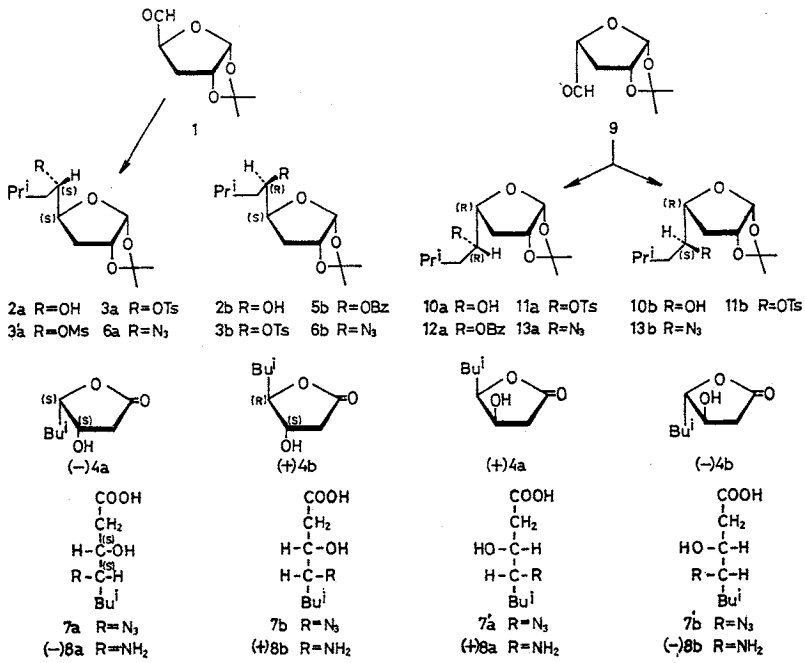
Sir:

A new amino acid, 4-amino-3-hydroxy-6-methylheptanoic acid (AHMHA) has been obtained by hydrolysis of pepstatin,[1~3] a specific inhibitor of acid proteases which UMEZAWA, *et al.* discovered in culture filtrates of Streptomycetes. In this paper, we wish to report the total synthesis of this amino acid and its stereochemistry which was unknown.

The GRIGNARD reaction of 3-deoxy-1, 2-O-isopropylidene-α-D-*erythro*-pentodialdo-1, 4-furanose (**1**)[4] with isobutylmagnesium bromide gave exclusively 3, 6-dideoxy-6-C-isopropyl-1, 2-O-isopropylidene-β-L-*lyxo*-hexofuranose (**2a**) in a 91 % yield, $C_{12}H_{22}O_4$*, mp 62.5~63.0°C, $[\alpha]_D^{19}$—33° (*c* 1.86, $CHCl_3$). The 5(S) configuration of **2a** was confirmed by the fact that hydrolysis of **2a** followed by oxidation with periodate-hypoiodite[5] afforded (3S, 4S)-3, 4-dihydroxy-6-methylheptanoic acid-1, 4-lactone, (—)**4a** ($C_8H_{14}O_3$,* $[\alpha]_D^{21}$—81° (*c* 1.12, MeOH)), the 4(S) configuration of which was determined by application of HUDSON's lactone rule ($\Delta[\alpha]_D$ (lactone-K salt) —36°).

Treatment of either the 5-O-*p*-tolylsulfonyl or the 5-O-methyl-sulfonyl derivative (**3a** and **3'a**) of **2a** with sodium benzoate in hot DMF gave a homogeneous S_N2 displacement product, 5-O-benzoyl-3, 6-dideoxy-6-C-isopropyl-1, 2-O-isopropylidene-α-D-*ribo*-hexofuranose (**5b**) in 33 % and 52 % yields, respectively, $C_{19}H_{26}O_5$*, $[\alpha]_D^{15}$ +17° (*c* 2.01, $CHCl_3$). Debenzoylation of **5b** afforded the 5-epimer **2b**, $C_{12}H_{22}O_4$*, mp 56.0~57.0°C, $[\alpha]_D^{18}$—10° (*c* 0.90, $CHCl_3$). The 5(R) configuration of **2b** was confirmed by conversion with periodate-hypoiodite of **2b** to epimeric (3S, 4R)-lactone, (+)**4b** ($C_8H_{14}O_3$*), with a rotation of $[\alpha]_D^{18}$+41° (*c* 1.73, MeOH) ($\Delta[\alpha]_D$ (lactone-K salt) +24°).

Treatment of 5-O-*p*-tolylsulfonyl derivative **3b** prepared from **2b** with sodium azide in hot DMF gave a homogeneous 5-azido compound **6a** as a sole displacement product in a 83 % yield, $C_{12}H_{21}O_3N_3$*, $[\alpha]_D^{18}$—63° (*c* 0.35, $CHCl_3$). The configuration of C-5 in **6a** was assumed to be "S", because a facile S_N2 displacement of the 5-*p*-tolylsulfonyloxy group of **3b** by azido ion would proceed under similar condition as S_N2



* Microanalyses agree with the molecular formula shown.

displacement of the corresponding group of **3a** by benzoate ion.

Based on the same principle, **3a** afforded epimeric 5(R)-azido compound **6b** in an 81.2% yield, $C_{12}H_{21}O_3N_3$*, $[\alpha]_D^{20}$+31° (*c* 1.88, $CHCl_3$).

Hydrolysis of **6a** with 50% acetic acid followed by succesive oxidation with sodium periodate and with sodium hypoiodite[5] gave a homogeneous azidohydroxy acid **7a** in a 32% yield, $\nu_{max}^{CCl_4}$ 2120 (N_3) and 1718 cm^{-1} (COOH). The azido acid **7a** was immediately hydrogenated on palladium black to afford (−) (3S, 4S)-4-amino-3-hydroxy-6-methylheptanoic acid (−)**8a** in a 90% yield, $C_8H_{17}O_3N$*, mp 201~203°C (dec.), $[\alpha]_D^{15}$−20° (*c* 0.64, H_2O). The synthetic amino acid (−)**8a** was proved to be identical with natural AHMHA** by mixture mp, optical rotation, NMR and IR criteria.

By the same procedure as that for the preparation of (−)**8a** from **6a**, the epimeric (+) (3S, 4R)-AHMHA (+)**8b** was obtained from **6b** *via* epimeric azidohydroxy acid **7b** in a 32% yield as colorless prisms, $C_8H_{17}O_3N$*, mp 202.5~203.5°C (dec.), $[\alpha]_D^{16}$+20° (*c* 0.66, H_2O).

The enantiomer (+)**8a** of the natural AHMHA (−)**8a** and the enantiomer (−)**8b** of the epimer (+)**8b** were also synthesized. GRIGNARD reaction of 3-deoxy-1, 2-O-isopropylidene-β-L-*threo*-pentodialdo-1, 4-furanose 9[6] with isobutylmagnesium bromide afforded, in this case, a mixture of two epimeric condensation products, which were separated from each other to give homogeneous 5-epimers, **10a** (30.9%) and **10b** (31.8%): **10a** ($C_{12}H_{22}O_4$*), $[\alpha]_D^{20}$+8° (*c* 1.3, $CHCl_3$); **10b** ($C_{12}H_{22}O_4$*), mp 76.0~77.5°C, $[\alpha]_D^{20}$−10° (*c* 1.0, $CHCl_3$). The C-5 configurations of **10a** and **10b** were determined as 5(R) and 5(S), respectively, by conversion to the corresponding epimeric 1, 4-lactones, (+)**4a** ($[\alpha]_D^{20}$+79° (*c* 1.3, MeOH)) and (−)**4b** ($[\alpha]_D^{18}$−40° (*c* 1.3, MeOH)), which were shown to be the enantiomers of the above-described (−)**4a** and (+)**4b**, respectively, by inspection of their optical rotations and NMR spectra.

It was also confirmed tha tthe 5-O-*p*-tolylsulfonyl derivative **11b** obtained from **10b** reacted with sodium benzoate in hot DMSO to afford only one isomer, 5-O-benzoyl derivative **12a** ($C_{19}H_{26}O_5$*, $[\alpha]_D^{14}$−47° (*c* 1.52, $CHCl_3$)), identical with that derived directly from **10a**. The yield was lower than that in the preparation of **5b** from **3a**.

Both *p*-tolylsulfonate **11b** and its epimer **11a** derived from **10b** thus underwent similar replacement with azide in hot DMSO to give, with inversion of configuration, homogeneous epimeric azido compounds, **13a** and **13b**, respectively: **13a** ($C_{12}H_{21}O_3N_3$*), 52.5%, mp 61.0~62.8°C, $[\alpha]_D^{19}$−85° (*c* 1.18, $CHCl_3$); **13b** ($C_{12}H_{21}O_3N_3$*), 38.7%, $[\alpha]_D^{14}$−56° (*c* 1.26, $CHCl_3$).

The epimers, **13a** and **13b** were converted to the corresponding azidohydroxy acids, **7'a** and **7'b**, which were hydrogenated to afford (+) (3R, 4R)-AHMHA (+)**8a** ($C_8H_{17}O_3N$*, mp 200~202°C (dec.), $[\alpha]_D^{19}$+19° (*c* 0.55, H_2O) and (−) (3R, 4S)-AHMHA (−)**8b** ($C_8H_{17}O_3N$*), mp 202~203°C (dec.), $[\alpha]_D^{18}$−20° (*c* 0.66, H_2O), respectively. IR and NMR spectra of (+)**8a** and (−)**8b** were identical with those of (−)**8a** and (+)**8b**, respectively.

Based on the synthetic results described above, we came to the conclusion that the absolute configuration of the natural AHMHA should be 3(S), 4(S). After this study we were informed by H. UMEZAWA that oxidation of dehydrated AHMHA with LEMIEUX's reagent gave L-leucine, indicating an "S" configuration of C-4.

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MITSUHIRO KINOSHITA
SHIMPEI ABURAKI
AKITO HAGIWARA
JIRO IMAI

Department of Applied Chemistry,
Faculty of Engineering,
Keio University,
Hiyoshi, Yokohama, Japan

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