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SYNTHESIS OF AVENIC ACID A AND 2'-DEOXYMUGINEIC ACID, AMINO ACIDS POSSESSING AN IRON CHELATING ACTIVITY

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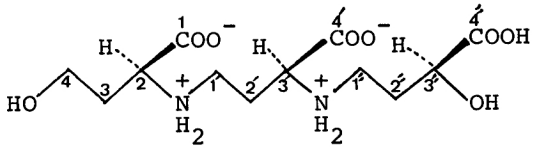
Avenic acid A (1), an amino acid derivative possessing an iron chelating activity and excreted from the root of Avena sativa L. was synthesized in optically active form by successive reductive coupling of protected L-aspartic β-semialdehyde and L-malic semialdehyde with L-homoserine lactone. 2'-Deoxymugineic acid (2), a related substance was also synthesized by the same method by which the stereostructure of this amino acid derivative was proved to be 2(S),3'(S),3"(S)-N-[3-(3-hydroxy-3-carboxypropylamino)-3-carboxypropyl]-azetidine-2-carboxylic acid.

Rice and oat plants cultured under iron deficient conditions excrete natural iron chelators from their roots to absorb iron ions in the chelated form.[1] Mugineic acid (3) is the first compound of such chelating agents isolated from the root washings of Hordeum vulgare L.[2] From the root excreta of Avena sativa L. cultured in iron less media, avenic acid A (1)[3] and 2'-deoxymugineic acid (2)[4] were isolated. Structure of avenic acid A was elucidated to be 2(S),3'(S),3"(S)-N-[3-(3-hydroxy-3-carboxypropylamino)-3-carboxypropyl]-homoserine (1) on the basis of the chemical and spectroscopic evidence. For 2'-deoxymugineic acid which has also been



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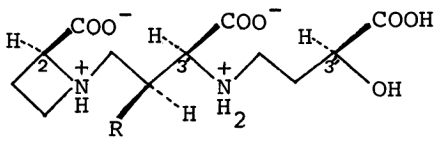


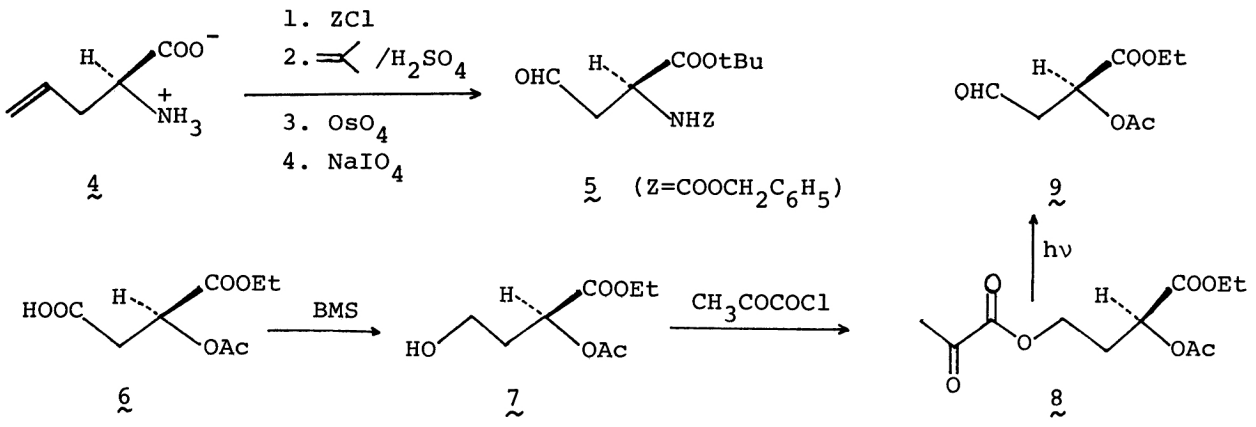
2: R=H
3: R=OH

isolated from Triticum aestivum L, the structure 2 with undefined stereochemistry at C-3" position has been given.[5]

Both avenic acid A (1) and 2'-deoxymugineic acid (2) have unique structural features which consist of two amino acids and one hydroxy acid moiety and each acid is linked by N-Cω linkage instead of the ordinary peptide bonds. Biogenetically, these derivatives such as 1 and 2 might be derived from three units of four-carbon amino acid or hydroxy acid by the reaction to form the N-Cω bond. As in many cases of alkaloid biosynthesis, a likely candidate for such a four-carbon unit in the formation of these trimeric substances could be assumed to be an amino-aldehyde such as aspartic β-semialdehyde (5) or malic semialdehyde (6) which can readily be linked under reductive conditions. To test the chemical validity of this assumption, we have achieved the synthesis of nicotianamine, L-azetidine-2-carboxylic acid dimer[6] and avenic acid B.[7] In the present communication, we describe the synthesis of avenic acid A (1) and 2'-deoxymugineic acid (2) by the same method. The latter synthesis has established the stereostructure of 2'-deoxymugineic acid to be 2(S), 3'(S),3"(S)-N-[3-(3-hydroxy-3-carboxypropylamino)-3-carboxypropyl]-azetidine-2-carboxylic acid.

The requisite L-aspartic β-semialdehyde derivative 5: $[\alpha]_D$ +15.1° (c 1.2, $CHCl_3$), pmr ($CDCl_3$) δ 9.73 (1H, br s), was prepared from L-allylglycine (4) in a 69% yield.[6] The second key compound, L-malic semialdehyde derivative 9[7] was synthesized by a route involving photoreduction[8] of the pyruvyl ester 8: ms, m/e 260 (M^+), pmr ($CDCl_3$) δ 2.16 (3H, s), obtained by reduction of the halfester 6 with borane methyl sulfide (BMS) followed by esterification for an overall yield of 51%.

Reductive coupling of L-homoserine lactone hydrobromide (10) with the protected aspartic β-semialdehyde (5) by using $NaBH_3CN$ at pH 6.0 afforded the lactone ester 11



in a 62% yield: $[\alpha]_D$ +2.3° (c 0.9, $CHCl_3$); ms, m/e 392 (M^+); ir ($CHCl_3$) 3430, 1773, 1715, 1700, 1498, 1370, 1342, 1151 cm^{-1}; pmr ($CDCl_3$) δ 1.45 (9H, s, $-C(C\underline{H}_3)_3$), 1.6-2.6 (4H, m, $C_{(3)}\underline{H}_2$, $C_{(2')}\underline{H}_2$), 2.6-3.0 (2H, m, $C_{(1')}\underline{H}_2$), 3.49 (1H, dd, J=8, 10, $C_{(2)}\underline{H}$), 4.0-4.5 (3H, m, $C_{(4)}\underline{H}_2$, $C_{(3')}\underline{H}$), 4.15 (1H, dd, J=6.5, 10, $C_{(3')}\underline{H}$), 5.08 (2H, s, $-OC\underline{H}_2-C_6H_5$), 5.68 (1H, d, J=7.5, $-N\underline{H}$), 7.32 (5H, s, $-C_6\underline{H}_5$). The amine 12 derived from the compound 11 by decarbobenzoxylation was then condensed with L-malic semialdehyde (9) by the action of $NaBH_3CN$ to give the lactone diester 13 in a 50% yield: $[\alpha]_D$ -23.0° (c 0.4, $CHCl_3$); ms, m/e 430.2357 (calc'd for $C_{20}H_{34}N_2O_8$, 430.2315); ir ($CHCl_3$) 3330, 1770, 1733, 1370, 1225, 1150 cm^{-1}; pmr ($CDCl_3$) δ 1.27 (3H, t, J=7, $-CH_2C\underline{H}_3$), 1.48 (9H, s, $-C(C\underline{H}_3)_3$), 1.6-2.3 (6H, m, $C_{(3)}\underline{H}_2$, $C_{(2')}\underline{H}_2$, $C_{(2")}\underline{H}_2$), 2.13 (3H, s, $-COC\underline{H}_3$), 2.3-3.0 (4H, m, $C_{(1')}\underline{H}_2$, $C_{(1")}\underline{H}_2$), 3.18 (1H, dd, J=5, 8, $C_{(3')}\underline{H}$), 3.56 (1H, dd, J=8, 10, $C_{(2)}\underline{H}$), 4.19 (2H, q, J=7, $-OC\underline{H}_2CH_3$), 4.1-4.5 (2H, m, $C_{(4)}\underline{H}_2$), 5.09 (1H, t, J=6.5, $C_{(3")}\underline{H}$). Deprotection and ring opening of the lactone ring of 13 was achieved by successive treatment with CF_3COOH and aq 1% KOH solution. Chromatographic purification on a Dowex 50W column furnished the compound 1: mp >300°C, $[\alpha]_D$ +15.5° (c 0.07, 2N HCl). The synthetic specimen was shown to be identical with natural avenic acid A (mp >300°C, $[\alpha]_D$ +16.4° (c 0.11, 2N HCl)) in all respects including the paper chromatography Rf value, Rt on HPLC, pmr and ir spectra.

Synthesis of optically active 2'-deoxymugineic acid (2)[9] was also performed by the same method as mentioned above. Reductive coupling of L-malic semialdehyde 9 with the amine diester 14[6] which, in turn, was obtained from L-azetidine-2-carboxylic acid and protected amino-aldehyde 5 in the presence of $NaBH_3CN$ gave the compound 15 in a 58% yield: $[\alpha]_D$ -51.6° (c 0.19, $CHCl_3$); ms, m/e 416.2151 (calc'd for $C_{19}H_{32}N_2O_8$, 416.2157); ir ($CHCl_3$) 3480, 1736, 1378, 1236, 1190 cm^{-1}; pmr ($CDCl_3$) δ 1.30 (6H, t, J=7, $-CH_2C\underline{H}_3$), 2.15 (3H, s, $-COC\underline{H}_3$), 3.77 (3H, s, $-COOC\underline{H}_3$), 5.13 (1H, t, J=6, $C_{(3")}\underline{H}$), 5.38 (1H, t, J=8, $C_{(2)}\underline{H}$). Treatment of the triester 15 with aq 1% KOH solution followed by chromatographic purification using Dowex 50W and Sephadex G-10 yielded the product 2 in an 80% yield: mp 196-200°C, $[\alpha]_D$-61.1° (c 0.13, H_2O) The synthetic sample of 2 was found to be identical with natural 2'-deoxymugineic acid (mp 198.5-200.5°C, $[\alpha]_D$ -70.5°) in all respects including PC and HPLC behavior patterns and ir and pmr spectra. The absolute configuration of chiral carbons of 2'-deoxymugineic acid was thus proved to be 2-(S), 3'-(S) and 3"-(S).

Synthesis of other trimeric amino acid derivatives from the four-carbon units such as 5 and 9 as well as biosynthetic studies concerning the possibility of the intermediacy of these four-carbon aldehydes in the formation of mugineic acid and avenic

acids are continuing.

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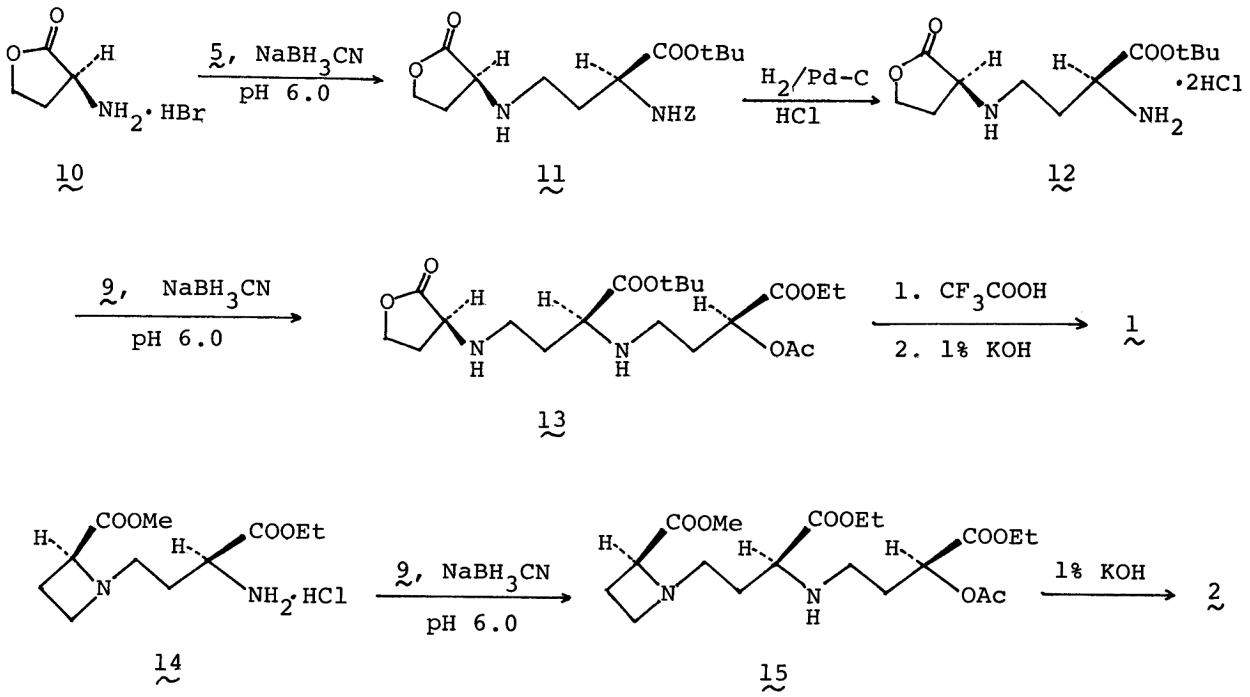

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