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SYNTHESIS OF (+)-AVENIC ACID A

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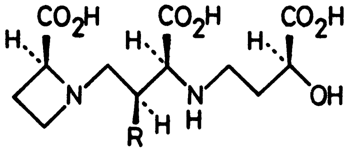
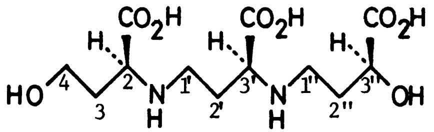
Avenic acid A (**2**), the metal chelator excreted from oat root and the factor which is considered to be directly involved in the uptake and transport of iron and other elements, has been synthesized efficiently from L-N[3-hydroxy-3-carboxypropyl]homoserine aldehyde, which could be a biosynthetic precursor.

Several metal chelating amino acid, e.g., mugineic acid(**1**) from barley(*Hordeum vulgare* L.),1) avenic acid A(**2**) from oat(*Avena sativa* L.),2) and 2'-deoxymugineic acid(**3**) from wheat(*Triticum aestivum* L.),3) which are regarded as factors responsible for the uptake and transport of metals have recently been isolated from the root washings of gramineous plants grown under iron-deficient conditions. Considerable effort is being directed towards clarification of the chelating properties,4) biological function5) and syntheses6) of these important compounds available in only restricted quantities from nature. The close similarity in the structure of 2S, 3'S, 3"S-avenic acid A(**2**) to that of mugineic acid(**1**) indicates that structure such as **4** based on X-ray studies of mugineic acid-Cu^{2+} complex4) in which six functionalities are used efficiently in chelation, are the forms responsible for physiological activities.



1 R=OH, **3** R=H



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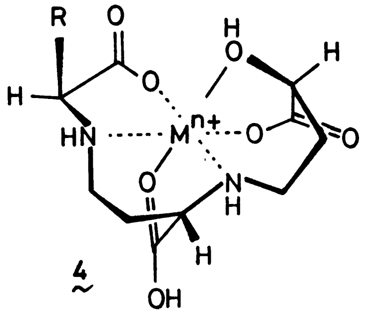

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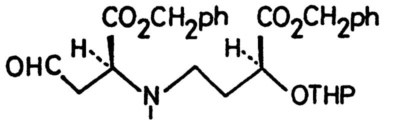
In the present report, we describe the biomimetic synthesis of natural (+)-avenic acid A(**2**) from the protected aldehyde **5**, an intermediate employed in the total synthesis of 2'-deoxymugineic acid(**3**).6a) Thus, L-tert-butoxycarbonyl-N[3-O-tetrahydropyranyl-3-carboxybenzylpropyl]homoserine aldehyde benzyl ester **5** (prepared from L-α-hydroxy-γ-butyrolactone in 21% yield, 9 steps) and L-homoserine lactone trifluoroacetate **6** were treated with NaBH$_3$CN in MeOH at room temperature for 14 h to give the protected avenic acid A lactone **7**,7) oil, 69%; IR(CHCl$_3$)1775, 1740, 1690 cm^{-1}; ^1H NMR($CDCl_3$ at 50 °C) δ7.32(s, 5H), 7.30(s, 5H), 5.14(s, 2H), 5.12 (s, 2H), 1.40(s, 9H). Hydrogenation with H_2/5% Pd-C, EtOH-H_2O(4:1), room temperature, 14 h, followed by treatment with CF_3COOH in CH_2Cl_2, room temperature, 0.5 h, gave in quantitative yield the lactone trifluoroacetate 8,[7] mp 48-50 °C; $[\alpha]_D^{23}$ -9.5°(c 0.44, H_2O), Hydrolysis with 2.5% KOH, room temperature, 14 h, afforded the potassium salt of 2, which upon treatment with Dowex 50W×4 resin(H^+ form), elution with 2N ammonia, and subsequent Sephadex G-10 chromatography yielded optically pure avenic acid A(2) in 80% yield. All physical constants of synthetic 2[8] were identical with those of natural (+)-avenic acid A.

It is conceivable that aldehyde 5 may well be the natural biosynthetic intermediate.[9] Preparations of metal chelates derived from (+)-avenic acid A and preparation of other compounds expressed by general formula 4 are in progress.[10]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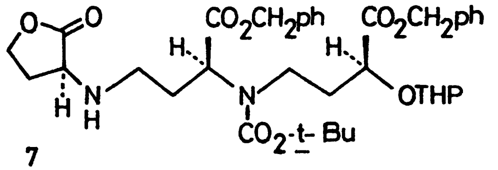
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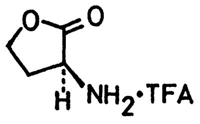
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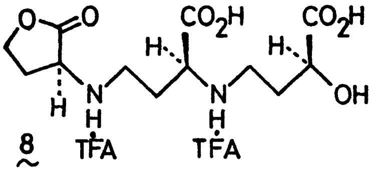
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References and Footnotes

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2) Fushiya, S.; Sato, Y.; Nozoe, S.; Nomoto, K.; Takemoto, T. Tetrahedron Lett., 1980, 3071.
3) Nomoto, K.; Yoshioka, H.; Arima, M.; Takemoto, T.; Fushiya, S.; Takagi, S. Helv. Chim. Acta., in press.
4) Nomoto, K.; Mino, Y.; Ishida, T.; Yoshioka, H.; Ota, N.; Takagi, S.; Takemoto, T. J. Chem. Soc., Chem. Commun., in press
5) Addition of either 1 or 3 to the culture medium of rice at pH 7 increased chlorophyll content.; Takagi, S.; to be published.
6) a) Ohfune, Y.; Tomita, M.; Nomoto, K. J. Am. Chem. Soc., in press; b) Quite recently, Nozoe et al., have succeeded in the synthesis of avenic acid A(2). Private communication from Professor S. Nozoe(Tohoku University, Japan).
7) Satisfactory elementary analytical data were obtained for these compounds.
8) (+)-Avenic acid A: ^1H NMR(360MHz)(1N NaOD) δ3.93(dd,1H, J=4.1, 7.8 Hz, C-3"H), 3.48(t, 2H, J=7.1 Hz, C-4H), 2.98(t, 1H, J=6.8 Hz, C-2H or C-3'H), 2.93(dd, 1H, J=6.0, 7.7 Hz, C-2H or C-3'H), 2.52(m, 1H), 2.30-2.45(m, 3H), 1.59-1.80(m, 5H), 1.48-1.59(m, 1H); CD(2N HCl) $\Delta\varepsilon_{209}$ +2.60(c 1.0).
9) Fushiya, S.; Sato, Y.; Nozoe, S. Chem. Lett., 1980, 1215.
10) We are indebted to Professor Koji Nakanishi, Director of Suntory Institute for Bioorganic Research, for discussions. We thank Professor Shigeo Nozoe, Tohoku University, for natural avenic acid A.

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