result was in full agreement with our hypothesis that III was electronically and stereochemically closest to the HEI (I). In order to check whether the neutral or the protonated amine was the inhibitory species, the derivative possessing a quaternary ammonium function VII was synthesized[9b] and used as inhibitor in the assay. The results (Figure 1) showed that VII was as strongly inhibitory as V, indicating that the charged species was probably the inhibitory one.

To our knowledge, this work demonstrates for the first time that a carbonium ion intermediate, involved in the biosynthesis of a sterol, can be mimicked by an ammonium group; such a result has important implications both in the search of new inhibitors and in our understanding of the molecular mechanisms involved in sterol biosynthesis.

As an example of the potential application of this class of compounds in vivo, III when given to bramble (*Rubus Fruticosus*) cell suspension growing in a liquid medium, was shown to inhibit drastically the sterol side chain methylation reactions resulting into a spectacular decrease of 24-ethyl sterols (major sterols in the control) and a correlative increase of 24-unalkylated sterols (not present in the control).[13] Thus III appears to be a molecular tool capable of manipulating in vivo the relative proportions of 24-methyl, 24-ethyl, and 24-unalkylated sterols in plant cells. Similarly 25-aza-24,25-dihydrozymosterol has recently been shown to block the C-24 methylation of zymosterol in *Saccharomyces cerevisiae*.[14,15]

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Total Synthesis of 2′-Deoxymugineic Acid, the Metal Chelator Excreted from Wheat Root

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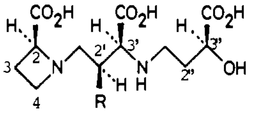
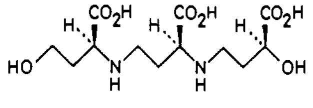
It is well-known that plants require many essential elements for their growth and maintenance; for example, iron is required in the biosynthesis of chlorophyll, and iron deficiency results in iron chlorosis.[1] Recently several amino acids possessing chelating properties for iron and other metals have been isolated from the root washing of gramineous plants grown under iron-deficient conditions.[2] Thus mugineic acid (1) has been isolated from barley (*Hordium vulgare* L.),[3] 2′-deoxymugineic acid (2) from wheat (*Triticum aestivum* L.),[4] and avenic acid A (3) from oat (*Avena sativa* L.).[5] It was demonstrated that addition of either 1 or 2 to the medium of water-cultured rice at pH 7 increases the chlorophyll content;[6] thus it is considered that they are involved in the uptake and transport of iron (and other elements) in higher plants. Structure 2 (with undefined stereochemistry at C-3″) was suggested for 2′-deoxymugineic acid on the basis of degradative studies and NMR comparisons with mugineic acid (1) of established structure.[4,7] The syntheses of these metal chelators are of both practical and academic interest in view of their biological roles, the minute quantity available, and the presence of multiple water-solubilizing functionalities in their structures. We report here the total synthesis of natural (−)-2′-deoxymugineic acid (2) *which establishes the configuration of chiral centers as 2S, 3′S, 3″S* (as shown in 2).

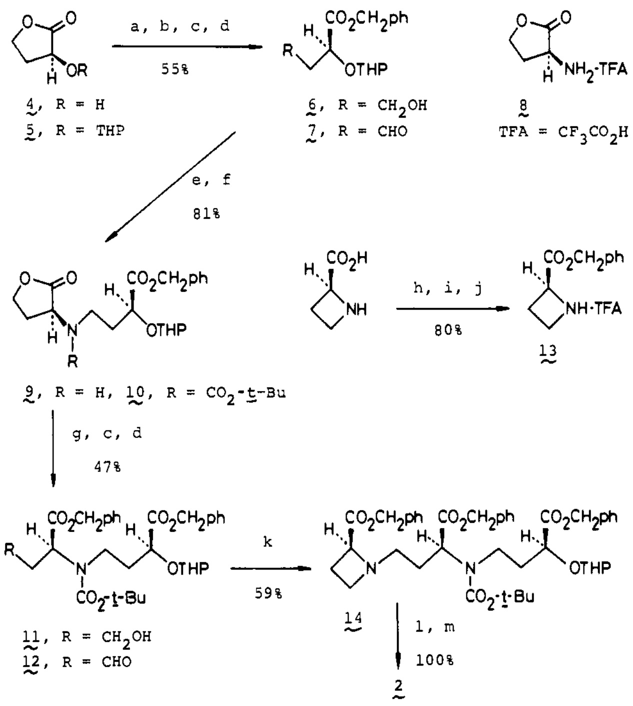


1, R = OH, 2, R = H



3

Scheme I[a]



[a] (a) DHP, TsOH, CH_2Cl_2, 0 °C, 30 min. (b) 2.5% KOH (1 equiv)-THF (1:1), room temperature, 1 h. (c) $PhCH_2Br$, 18-crown-6 (0.05 equiv), DMF-H_2O (4:1), room temperature, 6 h. (d) PCC, CH_2Cl_2, room temperature, 2 h. (e) 8, $NaBH_3CN$ (1.0 equiv), 0 °C (1 h), room temperature, 16 h. (f) $(t\text{-}BuOCO)_2O$, Et_3N (0.05 equiv), room temperature, 14 h. (g) 2.5% KOH (2 equiv)-dioxane (1:1), room temperature, 14 h. (h) Boc-ON, Et_3N, room temperature, 4 h. (i) 2.5% KOH (1 equiv), $PhCH_2Br$, 18-crown-6, DMF. (j) CF_3COOH, CH_2Cl_2, room temperature, 30 min. (k) 13, $NaBH_3CN$, MeOH, 0 °C (1 h), room temperature, 16 h. (l) H_2 (1 atm), 5% Pd-C, EtOH-H_2O (4:1), 1 N HCl (trace), 14 h. (m) CF_3COOH, room temperature, 1 h.

The structure of 2 reveals moieties derivable, either synthetically or biogenetically, from α-hydroxybutyric acid, homoserine, and the unique azetidine-2-carboxylic acid. Our synthetic plan for this molecule was to combine these three optically active units. The following crucial aspects had to be considered for the construction of 2′-deoxymugineic acid: (1) Only few methods exist for forming *N*-alkyl bonds in α-amino acids;[8] (2) mild reaction conditions are essential for each step to avoid racemization; (3) Selection of suitable protecting groups and deprotection at the

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final stage of synthesis are crucial, because of the presence of various water-solubilizing functionalities.

L-α-Hydroxy γ-butyrolactone (**4**),[9] readily available from L-malic acid, was converted (dihydropyran, *p*-toluenesulfonic acid, 0 °C) into a diastereomeric mixture of tetrahydropyranylated derivatives **5**[10] (95%) which were separated by chromatography[11] (Scheme I) [IR (neat) 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.49 (dd, 1 H, J = 8, 9 Hz), 4.27 (m, 2 H)]. Hydrolysis of **5** [2.5% KOH–THF (1:1), room temperature, 1 h], followed by benzylation [benzyl bromide, 18-crown-6, DMF–H_2O(4:1)] afforded γ-hydroxybenzyl ester **6**[10] (84%) [IR ($CHCl_3$) 3450, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 5.21 (d, 1 H, J = 12 Hz), 5.14 (d, 1 H, J = 12 Hz), 4.57 (dd, 1 H, J = 4.5, 9 Hz)]. Oxidation of **6** with pyridinium chlorochromate (PCC) in methylene chloride yielded L-malic half-aldehyde **7**[10] (72%) [IR ($CHCl_3$) 1738, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.76 (t, 1 H, J = 2 Hz), 7.34 (s, 5 H), 5.19 (s, 2 H), 4.84 (t, 1 H, J = 8 Hz), 2.86 (dd, 2 H, J = 2, 8 Hz)]. Coupling of half-aldehyde **7** and the homoserine moiety **8**[12] was achieved via a reductive amination procedure[13] (sodium cyanoborohydride, MeOH, room temperature, 14 h) and afforded the desired lactone amine **9**[10] in 90% yield [IR ($CHCl_3$) 3300, 1775, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 5.20 (d, 1 H, J = 12 Hz), 5.12 (d, 1 H, J = 12 Hz), 4.50 (t, 1 H, J = 7 Hz); mass spectrum, *m/e* 292 (M^+ – THP)]. Protection of **9** by using di-*tert*-butyl dicarbonate [Et_3N (0.05 equiv), CH_2Cl_2, room temperature, 14 h] gave the *tert*-butoxycarbonyl derivative **10**[10] (90%) [IR ($CHCl_3$) 1780, 1745, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$ at 50 °C)[14] δ 4.40 (dd, 1 H, J = 5, 8 Hz), 4.26 (dd, 1 H, J = 4, 9 Hz), 1.35 (s, 9 H)]. Successive treatment of **10** via the same sequence of reactions described above (**5** → **6**) gave rise to the dibenzyl ester **11**[10] in 63% yield [IR ($CHCl_3$) 3450, 1740, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$ at 50 °C)[14] δ 7.24 (s, 5 H), 7.22 (s, 5 H), 5.05 (s, 4 H)]. Azetidine-2-carboxylic acid was transformed into the trifluoroacetic acid salt of 2-benzyloxycarboxyl azetidine **13** via the following three-step sequence in 80% yield: (1) 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON), Et_3N, dioxane–H_2O (1:1); (2) 2.5% KOH (1 equiv), benzyl bromide, 18-crown-6, DMF; (3) CF_3COOH, room temperature, 30 min. PCC oxidation of **11** afforded the aldehyde **12**[10] (75%) [IR($CHCl_3$) 2725, 1743, 1735, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.76 (br s, 1 H)], which upon reductive amination with azetidine **13** yielded the protected 2′-deoxymugineic acid **14**[10], 59% yield [IR ($CHCl_3$) 1740, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$ at 50 °C)[14] δ 7.30 (s, 10 H), 7.27 (s, 5 H), 5.20 (d, 1 H, J = 12 Hz), 5.11 (s, 4 H), 5.06 (d, 1 H, J = 12 Hz), 1.35 (s, 9 H); mass spectrum, *m/e* 759 (M^+) + 1)]. All five protecting groups were removed under mild acidic conditions in two steps: (1) H_2, 5% Pd–C, EtOH–H_2O (4:1), 1 N HCl (trace); (2) CF_3COOH, room temperature, 1 h. The resultant trifluoroacetic acid salt was immediately treated with Dowex 50W-X4 ion exchange resin (H^+ form), eluted with aqueous ammonia, and chromatographed on Sephadex G-10 to afford optically pure 2′-deoxymugienic acid (**2**) as white crystals, mp 196–199 °C (lit.[4] 198.5–200.5 °C), 100% yield, $[\alpha]^{23}{}_{D}$ –66.6° (c 0.71) (lit.[4] –70.5°).

Synthetic **2**, which was obtained in 12% overall yield from lactone **4**, was identical in all respects (paper chromatography and IR, ^{1}H NMR, and ^{13}C NMR spectra) with the natural product. No racemization was encountered during the course of synthesis.[15] This study establishes both the structure and absolute configuration of 2′-deoxymugineic acid as that depicted in structure **2**. Further studies employing the synthetic specimen are in progress to clarify the mode of action of these metal chelators.

Acknowledgment. We are indebted to Professor Koji Nakanishi, Director of the Suntory Institute for Bioorganic Research, for discussions.

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(10) Oily compound. Satisfactory spectroscopic data as well as elementary analytical data were obtained for this substance.

(11) The synthesis was carried out with the THP derivatives rather than other derivatives despite the fact that they gave rise to a diasteromeric mixture; this was due to the ease of diastereomeric separation and deblocking. The synthetic sequence was carried through independently for both diastereomers which were readily separated by column chromatography (SiO_2), ether–hexane (3:2); the reactivity and yields of both series were comparable. The spectral data in the text refer to those for the less polar isomer. The intermediates possessed the following physical constants. Less polar compounds in $CHCl_3$: **5**, $[\alpha]^{23}{}_{D}$ –172° (c 1.17); **6**, $[\alpha]^{23}{}_{D}$ –117° (c 1.0); **7**, $[\alpha]^{23}{}_{D}$ –120° (c 1.05); **9**, $[\alpha]^{23}{}_{D}$ –100° (c 1.85); **10**, $[\alpha]^{23}{}_{D}$ –74° (c 0.85); **11**, $[\alpha]^{23}{}_{D}$ –74° (c 0.7); **12**, $[\alpha]^{23}{}_{D}$ –84° (c 1.2); **14**, $[\alpha]^{23}{}_{D}$ –97° (c 0.5). More polar compounds in $CHCl_3$: **5**, $[\alpha]^{23}{}_{D}$ +118° (c 0.98); **6**, $[\alpha]^{23}{}_{D}$ +20° (c 0.83); **7**, $[\alpha]^{23}{}_{D}$ +19° (c 1.33); **9**, $[\alpha]^{23}{}_{D}$ +20° (c 1.25); **10**, $[\alpha]^{23}{}_{D}$ +19° (c 1.05); **11**, $[\alpha]^{23}{}_{D}$ +8° (c 0.7); **12**, $[\alpha]^{23}{}_{D}$ +1° (c 0.6); **14**, $[\alpha]^{23}D$ –34° (c 2.0).

(12) Obtained by treatment of L-*tert*-butoxycarbonylhomoserine lactone with trifluoroacetic acid or L-homoserine in CF_3COOH at room temperature for 48 h.

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(14) Measurement at room temperature showed broad signals for this compound.

(15) Since each diastereoisomer **5**, **6**, and **10** (prepared by treatment with excess LDA) was cleanly separated in the high-pressure liquid chromatography (HPLC) (Waters Associates μ-Porasil column using $CHCl_3$ or $CHCl_3$–AcOEt system), the diastereomeric purity of compounds throughout the synthesis was examined to indicate homogeneous peaks. On the other hand, compounds **6**, **9**, **10**, and **11** were treated under the individual conditions described in the text to give no diastereoisomers even for longer reaction times.

Matrix Photolysis of Tetracarbonyldihydridoiron. Evidence for Oxidative Addition of Dihydrogen on Tetracarbonyliron

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The photolysis of transition-metal, organometallic hydrides can lead to ligand loss which may or may not be apparent from the stoichiometry of the products, metal–hydrogen bond cleavage, or dihydrogen loss in polyhydrides.[1-3] The matrix-isolation technique offers a unique method for studying these processes, because the reactive intermediates which form as the primary photoproducts can in many cases be preserved for spectroscopic study and identification. In this report, I show evidence of the loss of dihydrogen from $H_2Fe(CO)_4$ and the subsequent recombination (oxidative addition).

Oxidative addition reactions in matrices have rarely been reported. Methane oxidatively adds to metals under photolytic conditions.[4] Methane has also been shown to add to iron dimers under conditions in which it is not clear whether photolysis is required.[5] Heretofore, there have been no reports of dihydrogen oxidatively adding to a metal center at such low temperatures. That such reactions should occur with very small activation energies is not surprising, because the coordinatively unsaturated centers which undergo oxidative addition are themselves very short-lived. Processes which scavenge them must be fast in order to be significant.[6]

Figure 1 shows the matrix infrared spectrum of $H_2Fe(CO)_4$ isolated in Ar. The apparatus and techniques used to obtain matrices of unstable materials has been described previously.[2] The hydride was sublimed into a stream of argon at –127 °C and

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