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Efficient Synthesis of Mugineic Acid, A Typical Phytosiderophore, Utilizing the Phenyl Group as the Carboxyl Synthon[1]

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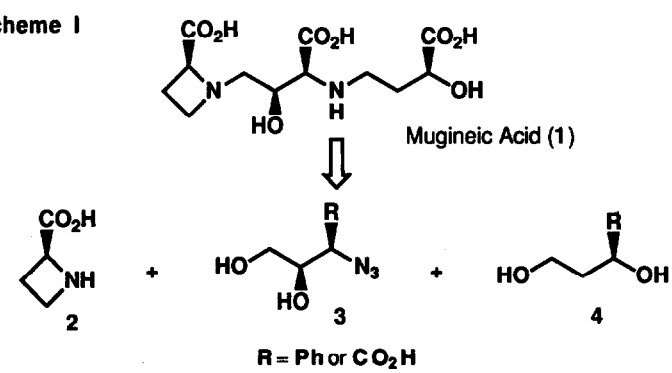
Abstract: Stereoselective total synthesis of mugineic acid, a unique phytosiderophore from roots of barley, has been achieved from (2R,3R)- and (2S,3S)-2,3-epoxycinnamyl alcohols employing the phenyl group as the carboxyl synthon.

Mugineic acid (**1**) is a typical phytosiderophore that is excreted from roots of barley and promotes uptake and transport of iron in higher plants.[2] Interestingly, it has been reported that mugineic acid exerts an inhibitory effect against angiotensin-converting enzyme.[2c] Although the synthesis of mugineic acid (**1**) has been reported from our laboratories,[3,4,5] their synthetic routes are not suitable for the large scale production of **1** because of their low yields and selectivity. We now report an efficient total synthesis of **1** which started from readily available (2R,3R)- and (2S,3S)-2,3-epoxycinnamyl alcohols[6] (**5** and **11**) employing the phenyl group as the carboxyl synthon.

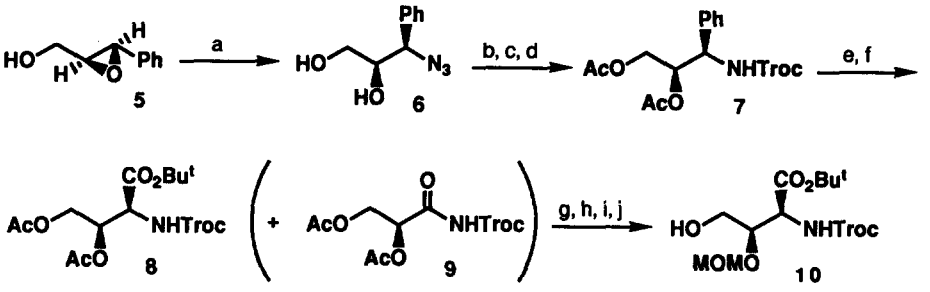
The retrosynthesis is outlined in Scheme I. Mugineic acid can be synthesized by coupling of the three fragments using reductive N-alkylation reaction.[7] The fragments **3** and **4** will be prepared from (2R,3R)- and (2S,3S)-2,3-epoxycinnamyl alcohols, respectively.[8,9] Conversion of the phenyl group to the carboxyl one can be achieved by oxidation with ruthenium trichloride-sodium metaperiodate.[10]

Scheme I



Preparation of the β-hydroxyhomoserine fragment is outlined in Scheme II. Treatment of (2R,3R)-2,3-epoxycinnamyl alcohol (**5**) with sodium azide according to the literature[8] afforded the azido alcohol **6**, $[\alpha]^{23}_{D}$ - 179.0° (c 0.88, $CHCl_3$), in quantitative yield. Reduction of the azide group, protection of the amino group with 2,2,2-trichloroethyl chlorocarbonate (TrocCl), followed

Scheme II

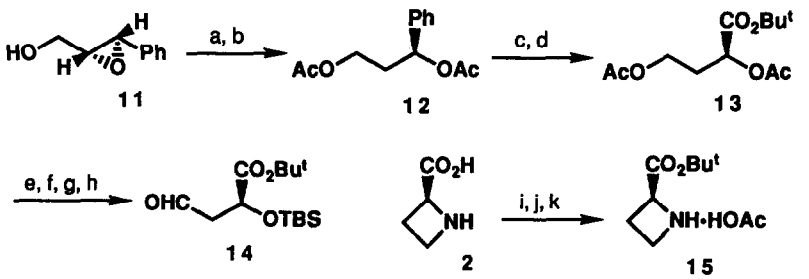


(a) NaN_3, NH_4Cl, MeOH, H_2O, 70°C, 10h. (b) 10% Pd-C, HCO_2NH_4, MeOH, rt, 1h. (c) TrocCl, $KHCO_3$, EtOAc, H_2O, rt, 1h. (d) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 19h. (e) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 24h. (f) O-tert-butyl-N,N'-diisopropylisourea, t-BuOH, CH_2Cl_2, 50°C, 6h. (g) Et_3N, MeOH, H_2O, -20°C, 3h then 0°C, 2h. (h) TBSCl, DMAP, Et_3N, CH_2Cl_2, rt, 20h. (i) MOMCl, i-Pr_2NEt, CH_2Cl_2, reflux, 17h. (j) AcOH, H_2O, rt, 24h.

by acetylation of the hydroxy group[11] afforded the fully protected phenylamine **7**, $[\alpha]^{25}_D$ - 34.0° (c 1.19, $CHCl_3$), in 93% yield from **6**. Oxidation of the phenyl group with ruthenium trichloride-sodium metaperiodate was performed with the improved method[12] of the literature,[10] followed by esterification of the resulting carboxylic acid with O-tert-butyl N,N'-diisopropylisourea[13] to give the β-hydroxyhomoserine t-butyl ester derivative **8**, $[\alpha]^{26}_D$ + 8.2° (c 0.80, $CHCl_3$), in 76% yield together with the overoxidation product **9**, $[\alpha]^{26}_D$ - 13.4 (c 1.10, $CHCl_3$), in 14% yield. Conversion of **8** to the alcohol **10** was performed in 4 steps. Deacetylation with triethylamine in aqueous MeOH, sequential protection of primary and secondary alcohols with t-butyldimethylsilyl (TBS) and methoxymethyl (MOM) groups, and desilylation of the TBS group afforded the alcohol **10**, $[\alpha]^{26}_D$ - 4.8° (c 0.89, $CHCl_3$), in 66% overall yield from **8**.

Preparation of the aldehyde fragment **14**, the right-hand constituent of **1**, is summarized in Scheme III. Reductive ring opening of (2S,3S)-2,3-epoxycinnamyl alcohol (**11**) was performed with sodium bis-methoxyethoxyaluminum hydride (Red-Al),[9] then acetylation of the diol function

Scheme III



(a) Red-Al, DME, 0°C, 0.5h then rt, 4.5h. (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 6h. (c) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 22h. (d) O-tert-butyl-N,N'-diisopropylisourea, CH_2Cl_2, rt, 18h. (e) Et_3N, MeOH, H_2O, -20°C, 8h. (f) TBSCl, imidazole, DMF, 50°C, 40h. (g) AcOH : THF : H_2O = 9:1:2, rt, 20h. (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C → 0°C, 2h. (i) ZCl, $NaHCO_3$, dioxane, H_2O, rt, 16h. (j) O-tert-butyl diisopropylisourea, CH_2Cl_2, reflux, 8h. (k) 10% Pd-C, H_2, EtOAc, rt, 1h, then addition of AcOH (1 eq.).

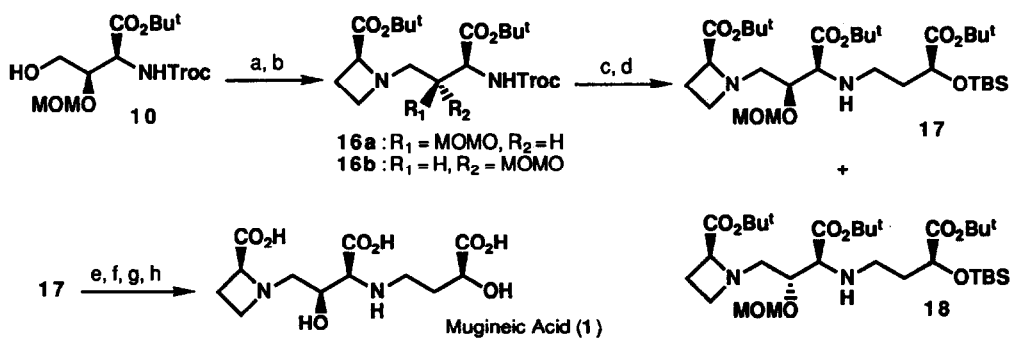
afforded the phenylpropanol derivative **12**, $[\alpha]^{22}_D$ - 54.1° (c 0.55, $CHCl_3$), in 81% yield. Transformation of the phenyl group to the carboxylic acid was performed via the same sequence of reactions described above (**7** → **8**) to give the t-butyl ester derivative **13**, $[\alpha]^{25}_D$ - 39.4° (c 1.11, $CHCl_3$), in 80% yield. Hydrolysis of the acetyl group of **13**, silylation of the diol function with TBSCl, selective desilylation of the primary protective group, and Swern oxidation afforded the aldehyde **14**, $[\alpha]^{24}_D$ - 37.1° (c 0.59, $CHCl_3$), in 52% yield.

(S)-Azetidinecarboxylic acid (**2**) was converted to its t-butyl ester in 3 steps according to the literature,[14] which was transformed to the acetic acid salt **15**, $[\alpha]^{24}_D$ - 37.9° (c 0.56, $CHCl_3$), in 85% yield from **2**, as shown in Scheme III.

Construction of **1** from each fragment described above (**10**, **14**, and **15**) is outlined in Scheme IV. Treatment of the alcohol **10** under Swern oxidation conditions followed by reductive N-alkylation with acetic acid salt **15** afforded an inseparable mixture of the key intermediate **16a** and its C-2' epimer **16b** in a ratio of 8:1 in 81% yield (91% conversion yield) along with recovery of the alcohol **10** in 12% yield. Removal of the Troc group with zinc in acetic acid followed by reductive N-alkylation with the aldehyde **14** afforded the protected mugineic acid **17**, $[\alpha]^{24}_D$ - 47.2° (C 0.89, $CHCl_3$), in 74% yield and its C-2' epimer **18**, $[\alpha]^{25}_D$ + 12.8° (c 0.69, $CHCl_3$), in 9% yield after column chromatographic separation. Removal of all the protecting groups of **17** with constant boiling hydrochloric acid in the presence of anisole followed by purification using Dowex 50W x 4 resin and ODS silica gel column chromatography afforded mugineic acid (**1**), mp 200 - 203°C (dec), $[\alpha]^{24}_D$ - 64.6 (c 0.43, H_2O), in 92% yield. The synthetic mugineic acid (**1**) was identical with the natural one by comparisons of spectra.[16]

Thus, we have completed an efficient synthesis of mugineic acid (**1**) in 15 steps in an overall yield of 29%, based on (2R,3R)-2,3-epoxycinnamyl alcohol (**5**). The overall procedures will be suitable for the large scale production of the unique phytosiderophore **1**. The methodology involving the use of the phenyl group as the carboxyl synthon will be useful for the synthesis of the other compounds of mugineic acid type.[17]

Scheme IV



(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78° C → 0°C, 2h. (b) **15**, 1M $NaBH_3CN$ in THF, MeOH, 0°C, 16h. (c) Zn, AcOH, THF, rt, 4h. (d) **14**, 1M $NaBH_3CN$ in THF, AcOH (1 eq), MeOH, 0°C, 3h then rt, 8h. (e) constant boiling HCl, anisole, THF, rt, 40h. (f) Dowex 50W x 4 (H_2O then 15% aqueous pyridine). (g) ODS silica gel, H_2O. (h) recrystallization from H_2O-EtOH.

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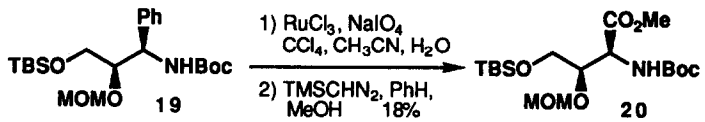
11. Protective group of the hydroxy function should be an electron-deficient one. An electron donating protective group (i.e., TBS or MOM) was not suitable for this oxidation system as shown below.



12. This oxidation can also be achieved with EtOAc instead of CCl_4 as the solvent.
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15. The ratio of epimers **16a** and **16b** was determined by 270 MHz ^{1}H-NMR.
16. ^{1}H-NMR spectra were measured in D_2O at pH=4.5 through the pH adjustment by the addition of DCl.[2b]
17. See the synthesis of 3-epi-hydroxymugineic acid and distichonic acid A in the following paper.

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