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Synthesis of Mugineic Acid through Direct C-Acylation Using Diphenyl Phosphorazidate[1,2]

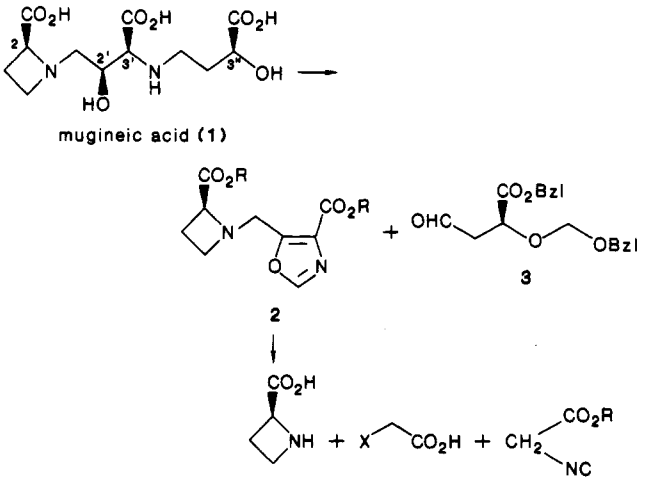
Summary: The first synthesis of mugineic acid, a typical phytosiderophore from roots of barley, has been achieved through direct C-acylation using diphenyl phosphorazidate (DPPA).

Sir: There has been considerable interest in new types of iron-chelating amino acids isolated from the root washings of gramineous plants.[3] They are called phytosiderophores, which promote uptake and transport of iron in higher plants. Mugineic acid[4] (1) is a typical phytosiderophore excreted from roots of barley. Its structure and iron transport mechanism have been well clarified by Nomoto and co-workers.[3a,c] Further investigations by Nomoto's group have recently revealed[5] that mugineic acid exerts an interesting inhibitory effect against angiotensin-converting enzyme. Although 2′-deoxymugineic acid, another phytosiderophore, was elegantly synthesized by Ohfune and co-workers,[6] there have been no reports to date on the synthesis of mugineic acid itself.

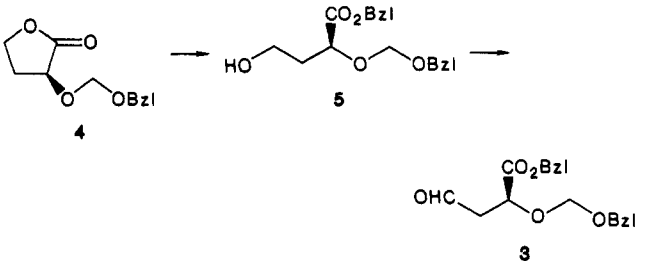
We now report the first synthesis of mugineic acid (1). Retrosynthetic analysis of 1, based on direct C-acylation using diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$) recently developed by our group,[7] revealed two building blocks as shown in Scheme I. One is the 4-(alkoxycarbonyl)oxazole 2 which will serve as a latent erythro β-hydroxy-α-amino acid[8] and be synthesized from (*S*)-azetidine-2-carboxylic acid, haloacetic acid, and isocyanoacetate. The other is the (*S*)-malic acid half-aldehyde derivative 3 which will constitute the right-half fragment of 1.

The known γ-lactone[9] 4 was converted to 3 in three steps as shown in Scheme II.[10] Hydrolysis of 4 with aqueous potassium hydroxide (1 equiv) in dimethylformamide–water (4:1) (room temperature, 2 h), followed by esterification with a mixture of benzyl bromide (1.5 equiv), 18-crown-6 (0.1 equiv), and potassium bicarbonate (1 equiv) (room temperature, 18 h), afforded the benzyl ester 5 as a colorless oil, $[\alpha]^{21}_D$ –61.8° (*c* 1, CH_2Cl_2). Treatment of 5 with sulfur trioxide–pyridine complex (3 equiv) and triethylamine (6 equiv) in dimethyl sulfoxide–methylene chloride (1:1) (10 °C, 30 min) gave the aldehyde 3 as a colorless oil, $[\alpha]^{23}_D$ –45.3° (*c* 1, CH_2Cl_2), in 70% yield. The

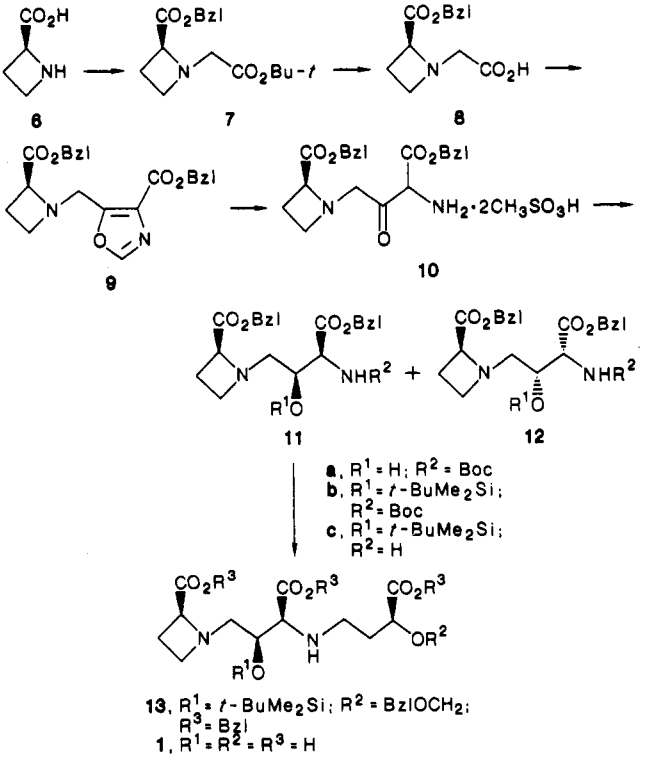
Scheme I



Scheme II



Scheme III



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synthetic route to **3** is essentially the same as the one employed for the synthesis of 2'-deoxymugineic acid.[6]

The left-half fragment of **1** was constructed from (*S*)-azetidine-2-carboxylic acid[11] (**6**), outlined in Scheme III.[10] Esterification of **6** was carried out by refluxing azeotropically with benzyl alcohol (4.8 equiv) and *p*-toluenesulfonic acid (1.2 equiv) in benzene (4 h). The crude product was directly N-alkylated with *tert*-butyl bromoacetate (1.5 equiv) in the presence of diisopropylethylamine (2.5 equiv) in tetrahydrofuran–benzene (1:1) (room temperature, 4 h), giving the diester **7** as a colorless oil, $[\alpha]^{21}_D$ −36.6° (*c* 1, MeOH), in 83% yield. Removal of the *tert*-butyl function of **7** with an excess of trifluoroacetic acid (room temperature, 2 h) afforded the amino acid **8**. Direct C-acylation[7,8] of benzyl isocyanoacetate (2 equiv) with the amino acid **8** smoothly proceeded by the use of DPPA (1.2 equiv) and potassium carbonate sesquihydrate (4 molar equiv) in dimethylformamide (0 °C, 2 h; room temperature, 40 h) to give the key intermediate oxazole **9** as a slightly yellow oil, $[\alpha]^{21}_D$ −56.1° (*c* 1, MeOH), in 80% yield from **7**.

Conversion of the oxazole function to the β-hydroxy-α-amino acid was achieved analogously to our prumycin synthesis.[8a] Treatment of **9** with methanesulfonic acid (10 equiv) in benzyl alcohol–water (10:1) (room temperature, 16 h) afforded the methanesulfonate of the α-amino ketone **10**, which was isolated by addition of diethyl ether followed by decantation. The crude product dissolved in ethanol was adjusted to pH 2 with 1 M sodium hydroxide in aqueous ethanol at −30 °C, cooled to −70 °C, and treated with sodium borohydride (1.5 molar equiv) in ethanol at −70 °C for 40 min. Quenching with 1 M hydrochloric acid followed by extractive workup afforded a diastereomeric mixture of the amino alcohols. Treatment of the mixture with di-*tert*-butyl dicarbonate (1.25 equiv) in chloroform (room temperature, 5 h) afforded a mixture of N-protected β-hydroxy-α-amino acid esters (**11a**, **12a**, and the other isomers), which were separated by column chromatography on silica gel with hexane–diethyl ether (1:2) to give two oily fractions, the less polar and the more polar isomers, in 19 and 44% yields, respectively. Although the major fraction was a mixture of two diastereomers and inseparable at this stage, the corresponding *tert*-butyldimethylsilyl derivatives obtained by treatment with *tert*-butyldimethylchlorosilane (2 equiv) and imidazole (6 equiv) in dimethylformamide (room temperature, 18 h) were separable by column chromatography on silica gel with hexane–diethyl ether (4:1), giving the more polar isomer as a colorless oil, $[\alpha]^{23}_D$ −11.9° (*c* 1, CH_2Cl_2), in 54% yield and the less polar isomer, $[\alpha]^{23}_D$ −15.9° (*c* 1, CH_2Cl_2), in 28% yield. From our result[8a] and the other[12] concerning reduction of α-acylamino acids, we assumed that the major isomer was (2'*S*, 3'*S*)-**11b** or (2'*R*, 3'*R*)-**12b** with erythro configuration. The ultimate proof for the structure **11b** assigned to the major isomer was obtained by converting to mugineic acid in three steps.

Thus, the *tert*-butyloxycarbonyl (Boc) group of the major isomer **11b** was first deprotected with trimethylsilyl trifluoromethanesulfonate[13] (3 equiv) in methylene chloride (0 °C, 1 h) under argon. The crude product **11c** was directly coupled with the right-half fragment **3** (1.1 equiv) by the use of sodium cyanoborohydride (1.45 equiv) in the presence of trifluoroacetic acid in isopropyl alcohol–tetrahydrofuran (5.6:3, pH 5) (room temperature, 17 h). The fully protected mugineic acid **13** was obtained in 75% yield as a colorless oil, $[\alpha]^{23}_D$ −17.1° (*c* 1, CH_2Cl_2). Final deprotection was achieved with methanesulfonic acid–anisole (10:1) (room temperature, 4 h), giving mugineic acid (**1**), mp 209–212 °C dec, $[\alpha]^{22}_D$ −62.5° (*c* 1, H_2O), in 71% yield. The synthetic material **1** was identical with the natural mugineic acid,[4] mp 210–212 °C dec, $[\alpha]_D$ −70.7° (*c* 0.97, H_2O), by IR, ^1H and ^{13}C NMR spectral, and chromatographic comparisons and exerted a parallel activity to that of natural one on inhibitory effect against angiotensin-converting enzyme.[5]

The above reaction sequence comprises a facile synthesis of mugineic acid in 11 steps from known and readily available (*S*)-azetidine-2-carboxylic acid (**6**) with an overall yield of 8.4%. Stereochemistry of the other isomers obtained by reduction of the α-acylamino acid ester **10** is now under investigation.

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Bis(neopentyloxy)triphenylphosphorane: A Versatile, Nonalkylating Cyclodehydration Reagent

Summary: Bis(neopentyloxy)triphenylphosphorane (BNTP; ^{31}P δ −58.3) is prepared in 48% yield by reaction of 2 equiv of lithium neopentoxide with dibromotriphenylphosphorane in anhydrous dichloromethane from −78 to 25 °C. BNTP smoothly converts a variety of diols, 2-aminoethanol, and 4-mercaptobutanol to the corresponding heterocycles in excellent yields (>95%) by ^{13}C and ^{31}P NMR analysis.

Sir: Quite recently, new emphasis has been placed on the synthetic potential of dioxytriphenylphosphoranes as mild, regioselective cyclodehydrating reagents for preparing a wide selection of oxygen,[1] nitrogen,[2] and sulfur[3] heterocycles. However, despite the relative ease of preparation of some dioxyphosphoranes [e.g., $Ph_3P(OEt)_2$ and $Ph_3P(OHex)_2$][1] by oxidative addition of alkyl peroxides to Ph_3P, the potential hazards associated with the preparation and use of peroxides (particularly, in large quantities)[4] serve

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