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Use of the aryl groups as the carboxyl synthon. Application to the synthesis of some natural products containing hydroxy amino acid functions

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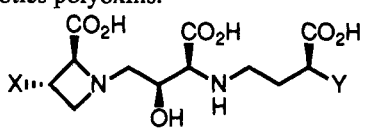
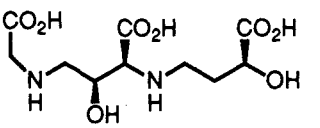
Abstract: The aryl groups are easily converted to the carboxyl group by oxidation with ruthenium tetroxide. Utilizing this transformation as a key step, several phytosiderophores (mugineic acid (**1**), 3-epi-hydroxymugineic acid (**2**), 2'-hydroxynicotianamine (**3**), and distichonic acid A (**4**)) and polyoxamic acid (**5**), the side chain moiety of the antifungal antibiotics polyoxins, have been efficiently and stereoselectively synthesized.

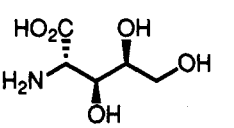
Reactivity and water solubility of the carboxyl group sometimes preclude the efficient and convenient synthesis of some natural products having the carboxyl functions. Since the carboxyl function will be easily formed by the oxidation of the aryl groups with ruthenium tetroxide, the temporary use of the aryl groups as a stable and non-reactive substitute for the carboxylic acid during the synthesis will be quite effective.

$$\mathbf{Ar} \equiv \mathbf{CO_2H} \quad (\ \mathbf{Ar} \xrightarrow{RuO_4} \mathbf{CO_2H}\ )$$

Utilizing this methodology, we have succeeded in the efficient, convenient, and stereoselective synthesis of some natural products containing hydroxy amino acid functions (1-3), which are shown below. Mugineic acid (**1**), 3-epi-hydroxymugineic acid (**2**), 2'-hydroxynicotianamine (**3**), and distichonic acid A (**4**) are the phytosiderophores while polyoxamic acid (**5**) is the side chain moiety of the antifungal antibiotics polyoxins.







mugineic acid (**1**) : X = H, Y = OH
3-epi-hydroxymugineic acid (**2**) : X = Y = OH
2'-hydroxynicotianamine (**3**) : X = H, Y = NH_2

distichonic acid A (**4**)

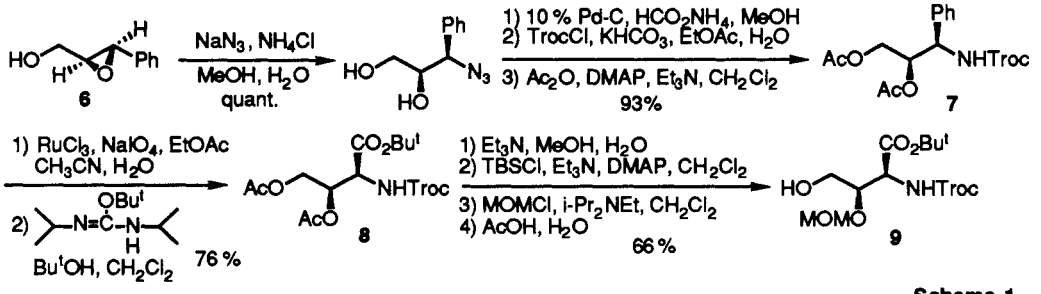
polyoxamic acid (**5**)

1. Phytosiderophores

The phytosiderophores produced in plants promote uptake and transport of iron required for the chlorophyll biosynthesis. Importance of the phytosiderophores in plant physiology as well as their unique amino acid structures have led us to synthesize them in an efficient manner suitable for the large scale production. In general, these phytosiderophores are composed of three parts, each of which is connected through the nitrogen atom. Thus, the three fragments should be synthesized first, and then the coupling of each fragment will follow to construct the whole molecule.

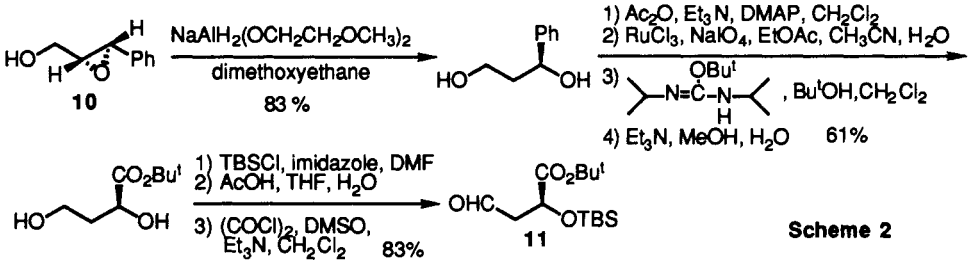
1.1 Mugineic Acid

Mugineic acid (**1**) is a typical phytosiderophore isolated from barley (*Hordeum vulgare* L. *var. Minorimugi*). Our synthesis (1) of the central fragment of **1** started from (2S,3S)-2,3-epoxycinnamyl alcohol (**6**), which was efficiently converted to the O,O'-diacetyl benzylamine derivative **7**, as shown in Scheme 1. Oxidation of the phenyl group with ruthenium tetroxide (prepared from ruthenium trichloride-sodium metaperiodate in situ), followed by tert-butyl esterification smoothly afforded the amino acid derivative **8**, which was converted to the required central fragment **9** through the four-step conversion.



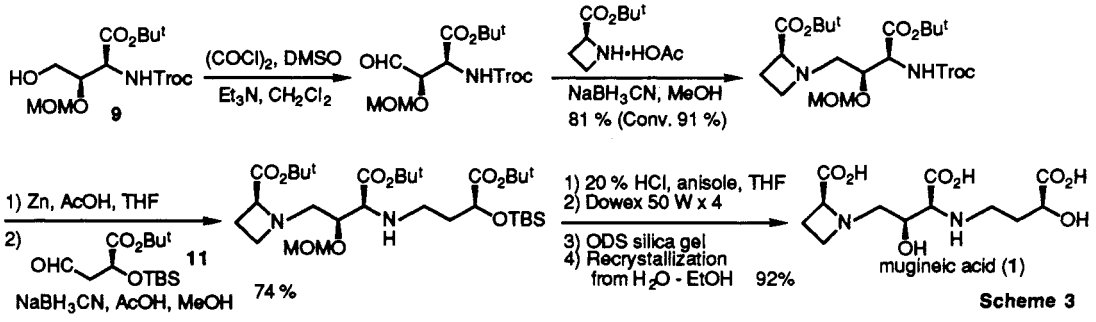
Scheme 1

Preparation of the right fragment **11** from (2R,3R)-2,3-epoxycinnamyl alcohol (**10**) is summarized in Scheme 2. Transformation of the phenyl function to the carboxyl one was analogously performed with ruthenium tetroxide.



Scheme 2

Assembling each fragment was accomplished through the sequential reductive alkylation by use of sodium cyanoborohydride, followed by deprotection to give mugineic acid (**1**), as outlined in Scheme 3. This synthesis of mugineic acid (**1**) consists of 15 steps from (2S,3S)-2,3-epoxycinnamyl alcohol (**6**) in an overall yield of 29 %, which will be suitable for the large scale production of **1**.

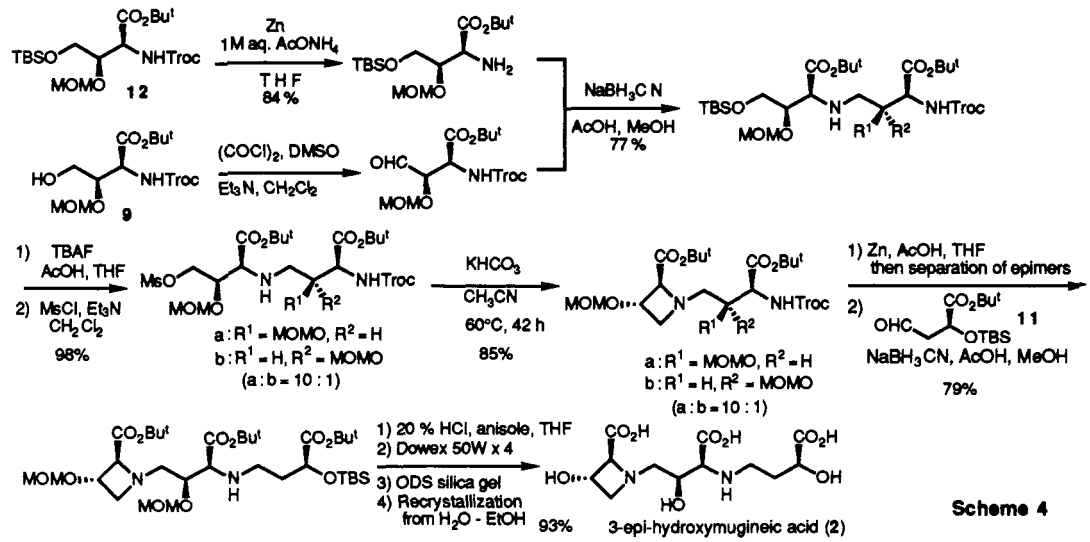


Scheme 3

1.2 3-Epi-hydroxymugineic Acid

3-Epi-hydroxymugineic acid (**2**) has been isolated from beer barley (*Hordeum vulgare* L. *var. distichum*). The β-hydroxy homoserine derivative **9** and its tert-butyldimethylsilyl(TBS) derivative **12**,

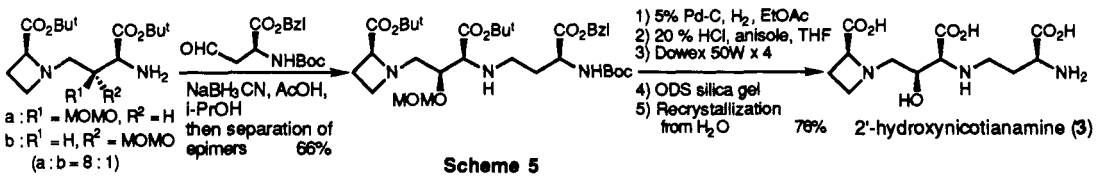
both of which have been the important intermediates for the synthesis of **1**, were used for the synthesis of **2**, as shown in Scheme 4 (2). The hydroxy-azetidine moiety was constructed from the methanesulfonyl (Ms) derivative under the basic conditions.



Scheme 4

1.3 2'-Hydroxynicotianamine

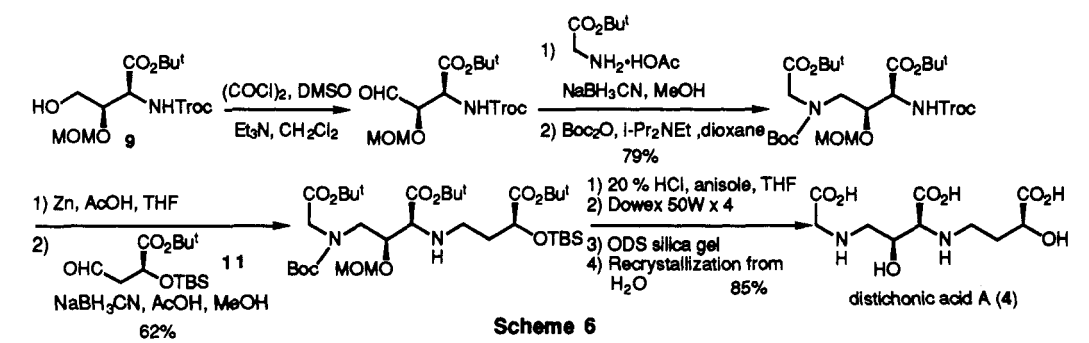
Although 2'-hydroxynicotianamine (**3**) has not been found in nature, its physiological action will be interested in comparison with that of mugineic acid (**1**). We synthesized **3** by use of the same intermediate for the synthesis of **1**, as outlined in Scheme 5 (2b).



Scheme 5

1.4 Distichonic Acid A

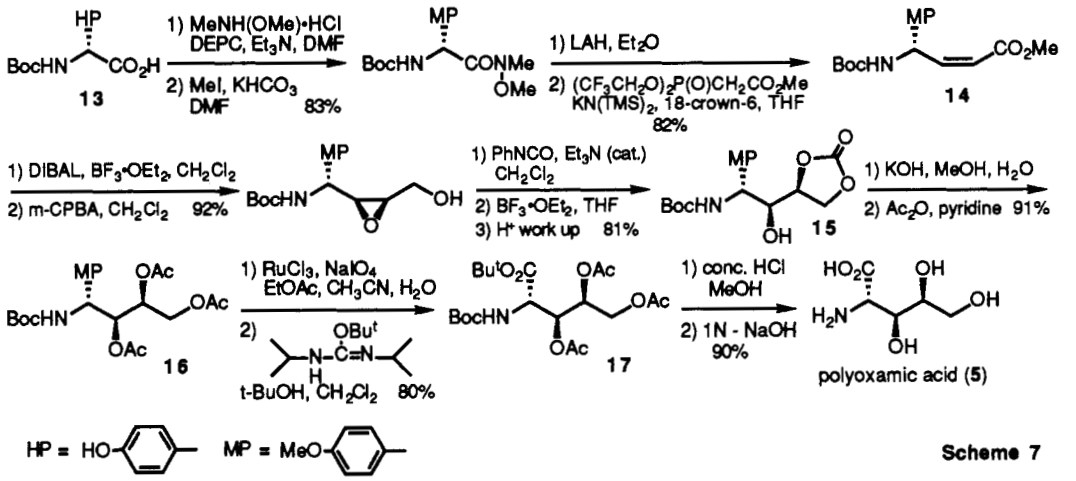
Distichonic acid A (**4**) was also isolated from beer barley (*Hordeum vulgare* L. *var distichum*). The left part of distichonic acid A (**4**) is composed of glycine instead of azetidine-2-carboxylic acid in mugineic acid (**1**). Thus, the synthesis of **4** was carried out from the same intermediate of the mugineic acid synthesis by use of glycine tert-butyl ester, as summarized in Scheme 6 (2).



Scheme 6

2. Polyoxamic Acid

Polyoxamic acid constitutes the side chain moiety of polyoxins which are a group of antifungal antibiotics isolated from *Streptomyces cacaoi var. asoensis*. As shown in the structure **5**, polyoxamic acid is a unique polyhydroxy amino acid. Our synthesis (3) of polyoxamic acid (**5**) started from N-tert-butoxycarbonyl(Boc)-(R)-4-hydroxyphenylglycine (**13**), which was converted to the cis-ester **14**, as shown in Scheme 7. Stereoselective epoxidation followed by the ring opening reaction afforded the lactone **15**, which was converted to the triacetate **16**. Ruthenium tetroxide oxidation of **16** afforded the carboxyl derivative **17** after tert-butyl esterification. Removal of the protective groups from **17** gave polyoxamic acid (**5**). Thus, we could accomplish an efficient synthesis of polyoxamic acid from Boc-(R)-4-hydroxyphenylglycine (**13**) in 13 steps in an overall yield of 30%.



Scheme 7

The above synthesis of the hydroxy amino acids **1-5** will well demonstrate the utility of the aryl groups as the carboxyl synthon. The methodology adopted in this work will have generality and will be useful for the efficient synthesis of the other polyhydroxy amino acids.

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3. F. Matsuura, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, in press.