Tetrahedron Letters, Vol. 33, No. 51, pp. 7921-7924, 1992
Printed in Great Britain

0040-4039/92 $5.00
Pergamon Press Ltd

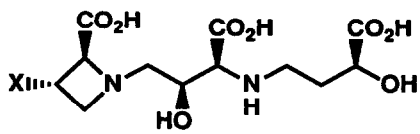
Efficient Synthesis of Phytosiderophores, 3-Epi-hydroxymugineic Acid and Distichonic Acid A

Fumiyoshi Matsuura, Yasumasa Hamada,* and Takayuki Shioiri*

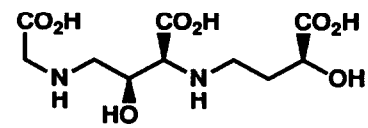
Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya 467, JAPAN

Abstract : Synthesis of 3-epi-hydroxymugineic acid (**2**) and distichonic acid A (**3**), phytosiderophores from graminaceous plants, has been efficiently achieved for the first time.

A series of iron-chelating amino acids has been isolated from graminaceous plants.[1] They are called phytosiderophores which promote uptake and transport of iron required for chlorophyll biosynthesis in higher plants. The most typical phytosiderophore is mugineic acid (**1**), which has been isolated from barley and well investigated its structural feature as well as its iron transport mechanism.[1,2] 3-Epi-hydroxymugineic acid (**2**)[1,3,4] and distichonic acid A (**3**)[1] are also phytosiderophores isolated from graminaceous plants. In our preceding paper,[5] we have described an efficient synthesis of mugineic acid (**1**)[6] utilizing the phenyl group as the carboxyl synthon. We now wish to report the first synthesis of 3-epi-hydroxymugineic acid (**2**) and distichonic acid A (**3**) by the analogous strategy.



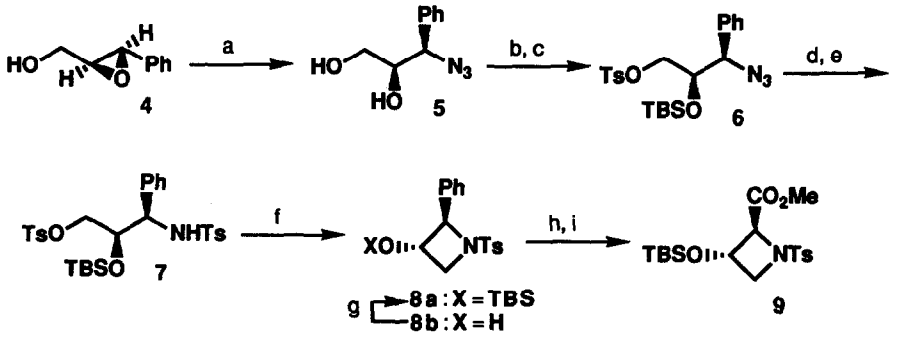
Mugineic Acid (**1**) : X = H
3-Epi-hydroxymugineic Acid (**2**) : X = OH



Distichonic Acid A (**3**)

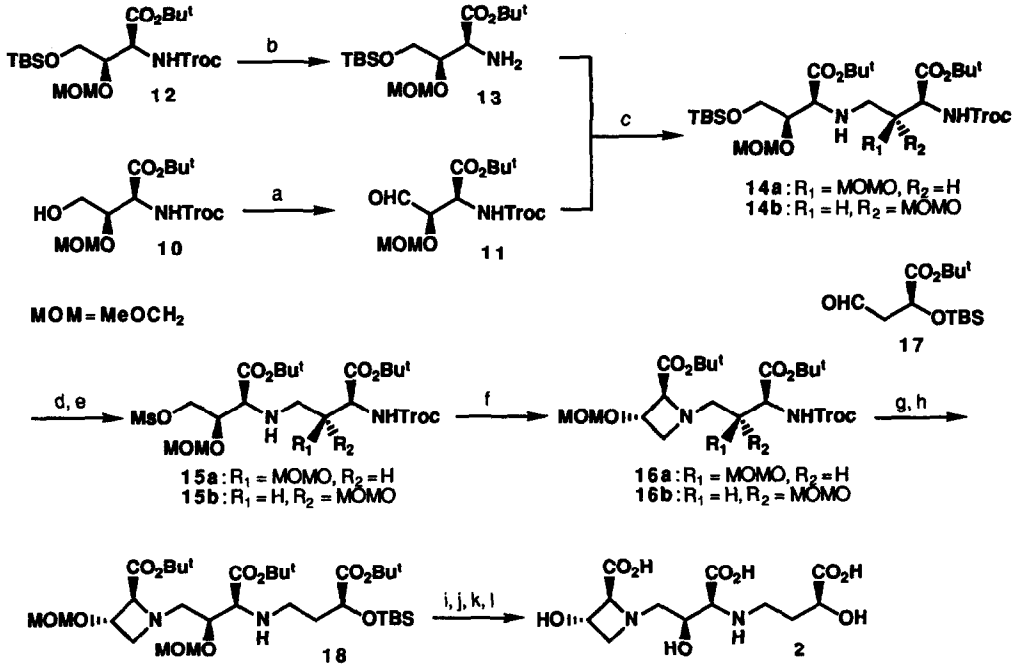
Prior to the synthesis of **2**, we first investigated the synthetic route to (3S)-hydroxy-azetidinecarboxylic acid, as shown in Scheme I. We employed (2R,3R)-2,3-epoxycinnamyl alcohol (**4**) as a starting material, which was quantitatively converted to the azido alcohol **5** according to our procedure reported in the preceding paper.[5] Sequential protection of the primary and secondary hydroxyl functions of **5** with p-toluenesulfonyl chloride (TsCl) and then tert-butyldimethylsilyl chloride (TBSCl) afforded the O,O-diprotected azide **6**. Transfer hydrogenation of **6** followed by tosylation of the resulting amine gave the N,O-ditosylate **7**, $[\alpha]^{25}_D$ - 15.2° (c 1.11, $CHCl_3$), in 22% yield from **4**. Treatment of **7** under basic conditions furnished the required azetidine **8a**, mp 103-108°C, $[\alpha]^{25}_D$ -145.7° (c 0.65, $CHCl_3$), in 75% yield, accompanied with the desilylated alcohol **8b**, mp 122-124°C, $[\alpha]^{25}_D$ - 185.3° (c 0.36, $CHCl_3$), in 18% yield. The latter was easily converted to the former by silylation with TBSCl in 99% yield. Oxidation of **8a** with ruthenium chloride-sodium periodate,[5,8] followed by methyl esterification with trimethylsilyldiazomethane ($TMSCHN_2$)[9] gave the azetidinecarboxylic acid derivative **9**, mp 67-69°C, $[a]^{25}_D$ - 56.2° (c 0.18, $CHCl_3$), in 42% yield.

Scheme I



(a) NaN_3, NH_4Cl, MeOH, H_2O, 70°C, 10h.[5] (b) TsCl, Et_3N, CH_2Cl_2, rt, 4h. (c) TBSCl, imidazole, DMF, rt, 19h. (d) 5% Pd-C, HCO_2NH_4, MeOH, rt, 1h. (e) TsCl, DMAP, Et_3N, CH_2Cl_2, rt, 3h. (f) NaH, MeOH, rt, 11h. (g) TBSCl, imidazole, DMF, 50°C, 3h. (h) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 40h. (i) $TMSCHN_2$, benzene, MeOH, rt, 10min.

Scheme II

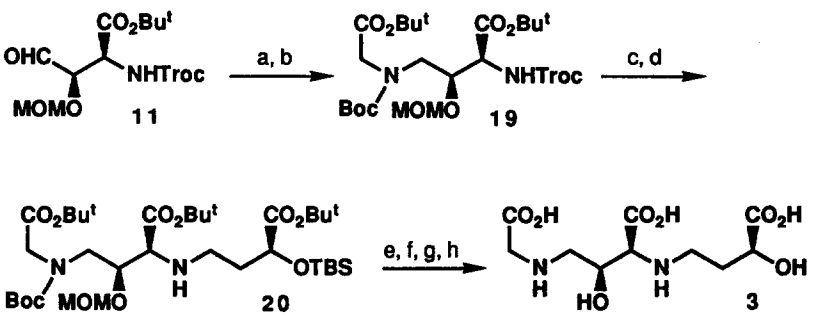


(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C → 0°C, 2h. (b) Zn, 1M aq. $AcONH_4$, THF, rt, 10h. (c) 1M $NaBH_3CN$ in THF, AcOH (1eq), MeOH, 0°C, 16h. (d) TBAF, AcOH, THF, rt, 17h. (e) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h. (f) $KHCO_3$, CH_3CN, 60°C, 42h. (g) Zn, AcOH, THF, rt, 13h. (h) **17**, 1M $NaBH_3CN$ in THF, AcOH (1eq), MeOH, 0°C, 14h. (i) constant boiling HCl, anisole, THF, rt, 24h. (j) Dowex 50W x 4 (H_2O then 15% aq. NH_3). (k) ODS silica gel, H_2O. (l) recrystallization from H_2O-EtOH.

With the above method for the azetidine moiety in hand, we started the synthesis of 3-epi-hydroxymugineic acid (**2**) from the alcohol **10** and the β-hydroxyhomoserine derivative **12** prepared in the preceding paper.[5] Swern oxidation of **10** afforded the aldehyde **11**, while the amine **13**, $[\alpha]^{25}_D$ + 32.9° (c 0.20, $CHCl_3$), was obtained in 84% yield from **12** by deprotection of its 2,2,2-trichloroethyloxycarbonyl (Troc) group with zinc, as shown in Scheme II. Reductive N-alkylation[5,10] of the amine **13** with the aldehyde **11** gave an inseparable mixture of the imino compound **14a** and its C-2' epimer **14b** in a ratio[11,12] of 10 : 1 in 77% yield. Exchange of the TBS function of **14** with the methanesulfonyl (Ms) one was smoothly accomplished to give the mesylates **15** in 98% yield by successive treatments with tetra-n-butylammonium fluoride (TBAF) and methanesulfonyl chloride (MsCl). Construction of the azetidine ring was easily achieved by heating the mesylates **15** at 60°C in acetonitrile in the presence of potassium hydrogen carbonate, giving the cyclized products **16a** and **16b** (ratio = 10:1) in 85% yield. Reductive removal of their Troc groups with zinc, separation of the C-2' epimer by silica gel column chromatography, and then reductive N-alkylation with tert-butyl 3-formyl-2-tert-butyldimethylsilyloxypropionate (**17**)[5] afforded 3-epi-hydroxymugineic acid in its protected form **18**, $[\alpha]^{25}_D$ - 43.2° (c 0.74, $CHCl_3$), in 79% yield. Removal of all the protecting groups of **18** by acid treatment, followed by purification as that of mugineic acid (**1**)[5] afforded 3-epi-hydroxymugineic acid (**2**), mp 181-184°C (dec), $[\alpha]^{24}_D$ - 33.2° (c 1.02, H_2O), in 93% yield.

A synthesis of distichonic acid A (**3**) was accomplished in a manner similar to that of **2**, as shown in Scheme III. Instead of the amine **13**, the acetic acid salt of glycine tert-butyl ester[13] was reductively coupled with the aldehyde **11**, giving the key intermediate **19**, $[\alpha]^{25}_D$ + 13.9° (c 0.55, $CHCl_3$), in 79% yield from the alcohol **5** after treatment with di-tert-butyl dicarbonate (Boc_2O). Treatment of **19** with zinc, followed by reductive N-alkylation with the aldehyde **17** afforded the protected derivative **20** of distichonic acid A (**3**), $[\alpha]^{24}_D$ - 17.5° (c 0.43, $CHCl_3$), in 62% yield. Deprotection of **20** performed by the same procedure as those for mugineic acid (**1**) and 3-epi-hydroxymugineic acid (**2**) afforded distichonic acid A (**3**), mp 200-201°C (dec), $[\alpha]^{24}_D$ + 3.16° (c 0.68, 1N HCl), CD $\Delta\varepsilon_{213nm}$ = +2.62 (c 4.0 x 10^{-4}M, 1N HCl), in 85% yield.

Scheme III



(a) AcOH•$H_2NCH_2CO_2Bu^t$, 1M $NaBH_3CN$ in THF, MeOH, 0°C, 12h. (b) Boc_2O, i-Pr_2NEt, dioxane, rt, 1h. (c) Zn, AcOH, THF, rt, 3h. (d) **17**, 1M $NaBH_3CN$ in THF, AcOH (1eq), MeOH, 0°C, 3h → rt, 11h. (e) constant boiling HCl, anisole, THF, rt, 14h. (f) Dowex 50W x 4 (H_2O then 15% aq. NH_3). (g) ODS silica gel, H_2O. (h) recrystallization from H_2O.

Thus we have efficiently achieved the first synthesis of two phytosiderophores, 3-epi-hydroxymugineic acid (**2**) and distichonic acid A (**3**). The synthetic methodologies adopted here will have generality in the synthesis of the other hydroxy amino acid derivatives. Furthermore, easy availability of these iron-chelating amino acids will be very helpful for the investigation of plant physiology.

Acknowledgment. We are grateful to the Japan Research Foundation for Optically Active Compounds, Foundation for the Promotion of Research on Medicinal Resources, and the Ministry of Education, Science and Culture for financial support of this work. F. M. gratefully acknowledges the postgraduate fellowship from the Japan Society for the Promotion of Science. We thank Dr. K. Nomoto of Suntory Institute for Bioorganic Research for the sample of **2**, spectra of **2** and **3**, and helpful discussions.

References and Notes

1. For reviews, see (a) Nomoto, K.; Ohfune, Y. *J. Synth. Org. Chem. Jpn.* **1982**, *40*, 401. (b) Ripperger, H.; Schreiber, K. *Heterocycles* **1982**, *17*, 447. (c) Sugiura, Y.; Nomoto, K. *Structure and Bonding* (Berlin) **1984**, *58*, 107.
2. (a) Takemoto, T.; Nomoto, K.; Fushiya, S.; Ouchi, R.; Kusano, G.; Hikino, H.; Takagi, S.; Matsuura, Y.; Kakudo, M. *Proc. Jpn. Acad. Ser. B* **1978**, *548*, 469. (b) Iwashita, T.; Mino, Y.; Naoki, H.; Sugiura, Y.; Nomoto, K. *Biochemistry* **1983**, *22*, 4842. (c) Murakami, T.; Ise, K.; Hayakawa, M.; Kamei, S.; Takagi, S. *Chem. Lett.* **1989**, 2137 and references therein. (d) Kawai, S.; Itoh, K.; Takagi, S.; Iwashita, T.; Nomoto, K. *Tetrahedron Lett.* **1988**, *29*, 1053.
3. Nomoto, K.; Yoshioka, H.; Takemoto, T.; Fushiya, S.; Nozoe, S.; Takagi, S. Abstract of papers, 22nd Symposium on the Chemistry of Natural Products, Fukuoka, October **1979**, p. 619.
4. The absolute configurations at the C-3 position of 3-hydroxymugineic acid and its C-3 epimer are rather confusing. We adopt here Dr. K. Nomoto's view that 3-epi-hydroxymugineic acid has (3S)-configuration (Private communication from Dr. K. Nomoto).
5. Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* the preceding paper.
6. (a) For the first synthesis, see Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1986**, *51*, 5489. (b) For the formal synthesis, see Hamada, Y.; Iwai, K.; Shioiri, T. *Tetrahedron Lett.* **1990**, *31*, 5041 and Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron : Asymmetry* in press. (c) For the approach toward **1**, see Carreaux, F.; Duréault, A.; Depezay, J.C. *Synlett* **1992**, 527.
7. Cf. Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M.A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6935.
8. (a) Carisen, P.H.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Nuñez, M.T.; Martin, V.S. *J. Org. Chem.* **1990**, *55*, 1928.
9. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.
10. (a) Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Ohfune, Y.; Tomita, M.; Nomoto, K. *J. Am. Chem. Soc.* **1981**, *103*, 2409.
11. Ratio of the epimers was determined by 270 MHz ^{1}H-NMR.
12. The ratio of epimers (10:1) was slightly different from the precedent result (8:1).[5] This might be due to the differece of the reactivity between the imino group (azetidine moiety in the precedent paper) and the amino group of **13**.
13. Chimiak, A.; Kolasa, T.; Biernat, J.F. *Z. Chem.* **1972**, *12*, 264.

(Received in Japan 28 August 1992)