Tetrahedron Letters, Vol.31, No.35, pp 5041-5042, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A NEW STEREOSELECTIVE SYNTHESIS OF A γ-AZETIDINYL-β-HYDROXY-α-AMINO ACID MOIETY OF MUGINEIC ACID — A FORMAL SYNTHESIS OF MUGINEIC ACID[1]

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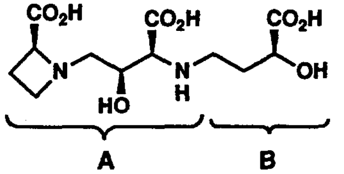
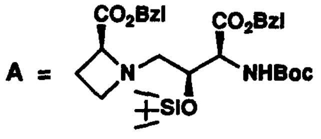
Abstract: A γ-azetidinyl-β-hydroxy-α-amino acid moiety of mugineic acid (1) was stereoselectively prepared as its protected form 2 from (R)-glyceric acid derivative 3, providing an alternative synthesis of mugineic acid (1).

Mugineic acid (1) excreted from roots of barley is a typical phytosiderophore which promotes uptake and transport of iron in higher plants. We have already achieved[2] the first total synthesis of this unique iron-chelating amino acid. We now report an alternative stereoselective synthesis of a γ-azetidinyl-β-hydroxy-α-amino acid moiety **A** as its protected form **2**, a key intermediate for our former synthesis of **1**.[2] The overall process will be more suitable for the large scale production of the amino acid important in plant physiology.



mugineic acid (1)



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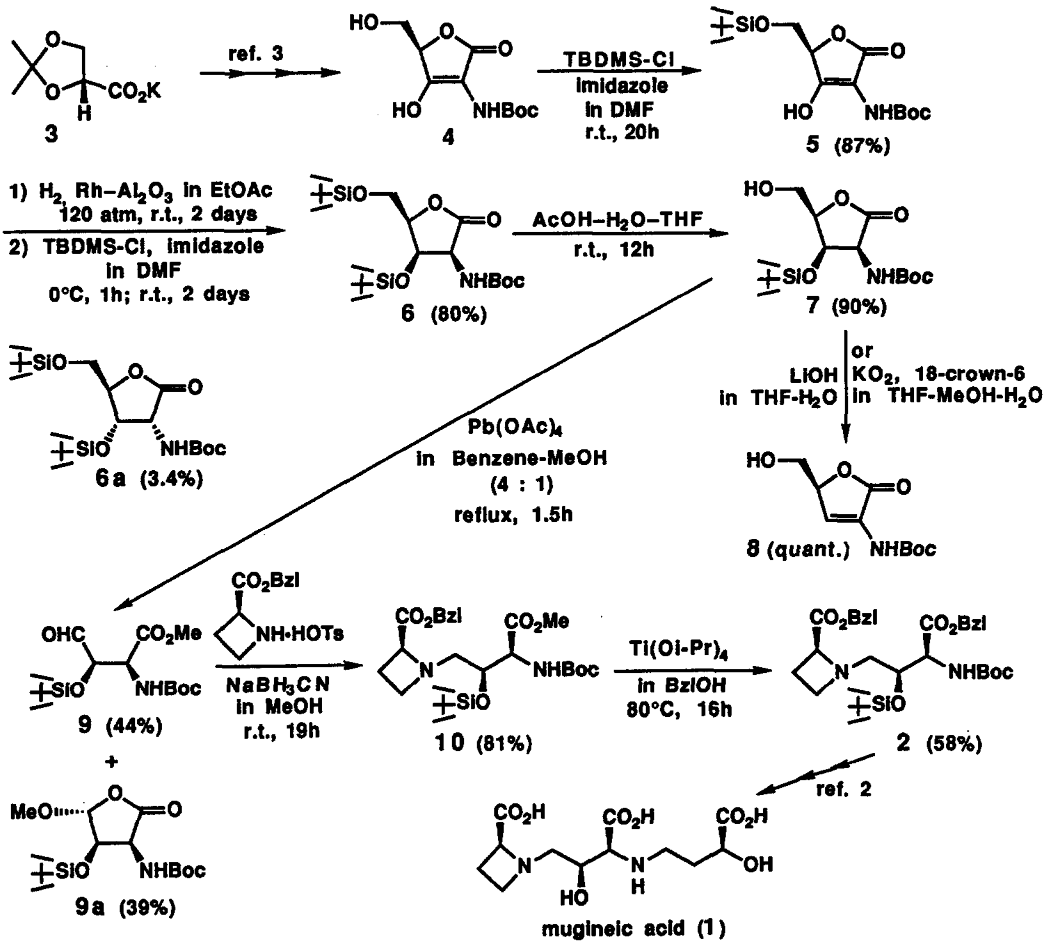
(R)-3-tert-Butoxycarbonyl-5-hydroxymethyltetronic acid (**4**), prepared from the potassium salt of O,O'-isopropylidene-(R)-glyceric acid (**3**) according to our procedure,[3] was selectively silylated at the primary alcohol function with tert-butyldimethylsilyl chloride (TBDMS-Cl). Selective catalytic hydrogenation of the monosilylated compound **5**, mp 98.5 - 100°C, $[\alpha]^{21}_D$ +61.4° (c=1.01, MeOH), over rhodium - alumina, followed by silylation with TBDMS-Cl afforded the D-lyxo-1,4-lactone **6** as a colorless oil, $[\alpha]^{27}_D$ +37.8° (c=0.96, CH_2Cl_2), in 80% yield together with a small amount (3.4% yield) of the D-ribo isomer **6a**, mp 96 - 98°C, $[\alpha]^{27}_D$ -8.6° (c=1, CH_2Cl_2). Treatment of **6** with acetic acid-water-tetrahydrofuran selectively desilylated at the primary alcohol function to give the lactone alcohol **7**, a colorless oil, in 63% overall yield from **4**.

Attempts to open the lactone ring of **7** under alkaline conditions quantitatively yielded the elimination product **8** as a colorless oil.[4] However, treatment of **7** with lead tetraacetate in benzene-methanol (4 : 1) under reflux for 1.5h afforded a mixture of the aldehyde **9**, a colorless oil, in 44% yield and the methyl ether **9a**, a colorless oil, in 39% yield.[5]

The aldehyde **9** easily underwent the reductive amination with the p-toluenesulfonate salt of benzyl (S)-2-azetidinecarboxylate by use of sodium cyanoborohydride, giving the oily methyl ester **10**. The methyl ester function of **10** was exchanged with the benzyl ester group by use of titanium isopropoxide in benzyl alcohol,[6] giving the protected form **2**, a colorless oil, of the desired γ-azetidinyl-β-hydroxy-α-amino acid moiety **A** of mugineic acid (**1**). Since we have been already able to transform **2** to mugineic acid (**1**),[2] this synthesis provides an alternative synthesis of the unique iron-chelating amino acid **1**.



References and Notes

1. New Methods and Reagents in Organic Synthesis. 90. For Part 89, see M. Kohmori, H. Daiki, Y. Komase, M. Goto, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, submitted.
2. Y. Hamada and T. Shioiri, *J. Org. Chem.*, **51**, 5490 (1986).
3. a) A. Kawai, O. Hara, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, **29**, 6331 (1988). b) Y. Hamada, A. Kawai, T. Matsui, O. Hara, and T. Shioiri, *Tetrahedron*, in press.
4. For the analogous elimination, see the reference 3b.
5. The glycol cleavage is rather tricky, and methanol could not be replaced with water, isopropanol, tert-butanol, benzyl alcohol, neopentyl alcohol, trityl alcohol, and trimethylsilanol. However, trichloro and trifluoroethanols afforded the ethers corresponding to **9a** in more than 70% yield. Use of ethanol yielded a mixture of the aldehyde **9** (28% yield) and the ethyl ether (23% yield), while methoxyethanol produced the methoxyethyl ether (32% yield) only.
6. D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann, and M. Züger, *Synthesis*, 138 (1982); H. Rehwinkel and W. Steglich, *Synthesis*, 826 (1982).

(Received in Japan 1 June 1990)