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A Novel Synthetic Approach Towards Phytosiderophores: Expeditious Synthesis of Nicotianamine and 2'-Deoxymugineic Acid

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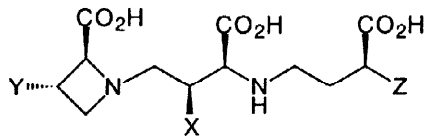
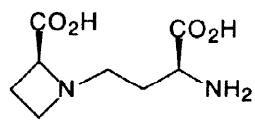
Abstract: A short and a novel approach for synthesis of nicotianamine, 2'-deoxymugineic acid and related phytosiderophores has been achieved through peptide intermediates. Selective amide reduction in the presence of ester functionalities by conversion to thioamide and subsequent desulfurization with Raney nickel were employed as key reactions.

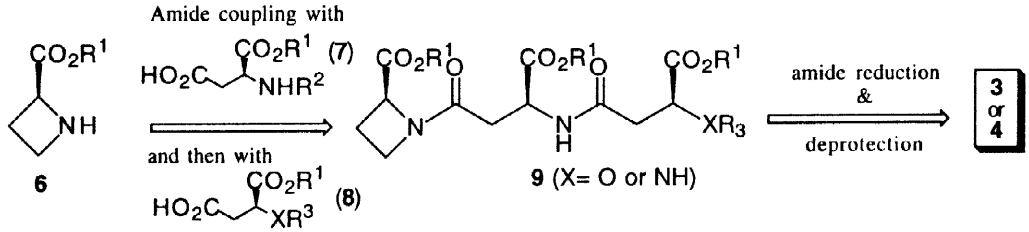
Phytosiderophores, for ex.(**1-4**), produced in higher plants as iron chelating amino acids promote uptake of iron from soil.[1] The role of phytosiderophores is significant in plant physiology and has led several groups to synthesize them.[2,3] A comprehensive review of the previous syntheses is reported.[3] The aim of the current work was to attempt a novel approach for an efficient synthesis of these compounds via peptide intermediates to afford structurally diverse phytosiderophores with sufficient amount of material for biological study. Our synthetic strategy towards **3** and **4** is illustrated in Scheme 1. It was anticipated that the amine **6** could be coupled to a suitably protected L-aspartic acid unit **7** to give dipeptide. Selective deprotection of R^2 group in the resulting dipeptide and a second coupling reaction with another protected unit of L-aspartic acid or L-malic acid unit **8** to give tripeptide **9**.



1 Mugineic acid : X=Z=OH, Y=H
2 3-Epi-hydroxy mugineic acid : X=Y=Z=OH
3 2'-Deoxymugineic acid : X=Y=H, Z=OH
4 Nicotianamine :X=Y=H, Z=NH_2



5 *N*-(3-Amino-3-carboxypropyl) azetidine -2-carboxylic acid



Scheme 1

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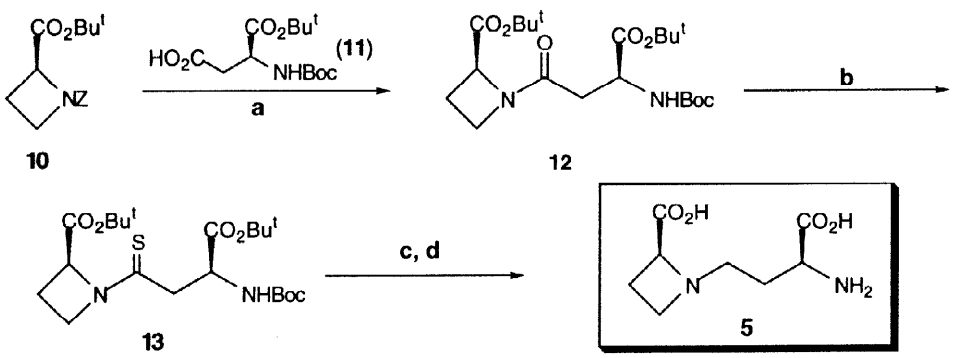
In all of the previous syntheses, reductive alkylation step was adopted for the coupling of each amino acid moiety. We assumed that it should be more efficient and simpler if the selective reduction of amide group of the tripeptide **9** is realized. Selective amide reductions in the presence of esters with, for example borane reagents are often unselective.[4] However, amides have indeed been converted to amines in the presence of borane sensitive functionalities by conversion to thioamides followed by desulfurization with Raney nickel.[5] We hoped to extend this method to tripeptide **9** and subsequent deprotection of resulting diamine triester to furnish the desired phytosiderophores.

Based on this strategy we successfully prepared the nicotianamine model compound **22** (see ref. 15). We then moved onto synthesis of *N*-(3-amino-3-carboxypropyl)azetidine-2-carboxylic acid **5** (Scheme 2), which was first isolated from the seeds of *Fagus silvatica L* which also contain nicotianamine.[6a] The known compound **10**[7] was hydrogenated and the unstable crude product was treated immediately under *O*-benzotriazolyl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) amide coupling conditions[8] with the acid **11**[9] to obtain dipeptide **12**. Thionation with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulphide[10] (Lawesson's reagent) gave corresponding endothiopeptide **13**. Desulfurization of **13** by reaction with Raney nickel and final deprotection with TFA and Dowex purification furnished the desired product **5**; $[\alpha]_D^{20}$ -79.6°(c 0.4, H_2O) [lit.[6a]: $[\alpha]_D^{20}$ -79° (c 1, H_2O), lit.[6c] : $[\alpha]_D$ -81.8°(c 0.06, H_2O)]. The spectral characteristics were matching with the literature data. (39% overall yield in 5 steps)

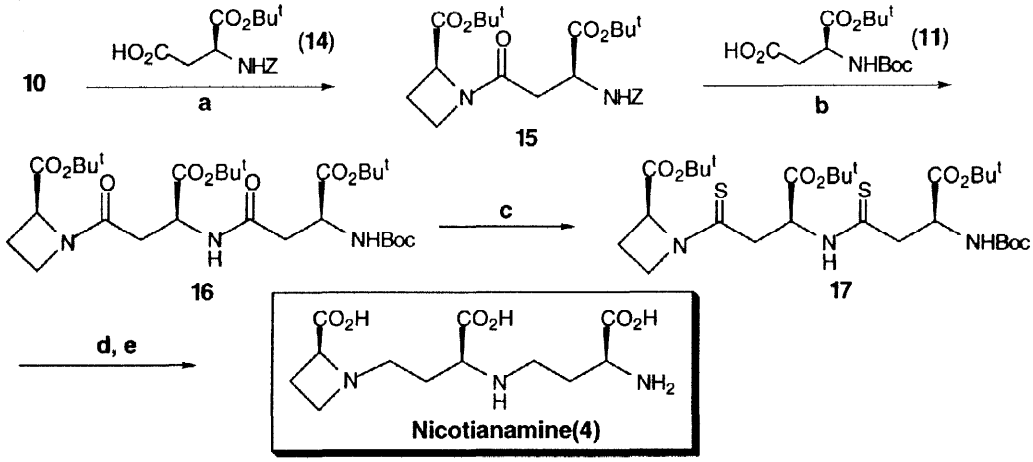


Scheme 2

a) i) H_2, Pd/C, EtOAc. ii) **11**, HBTU, *N*-Ethylmorpholine, MeCN, 64%. b) Lawesson's reagent, C_6H_6, 55° C, 16 h, 72%. c) Raney nickel (W-2), EtOH, 50° C, 3h, 85%. d) TFA & then Dowex purification, quant.

The synthesis of nicotianamine was carried out as shown in Scheme 3. Catalytic hydrogenation of **10** and immediate coupling with the known acid **14**[11] gave dipeptide **15** in 69% yield. The hydrogenation and coupling with the acid unit **11** was repeated to afford tripeptide **16**. The tripeptide **16** on reaction with Lawesson's reagent gave **17** followed by desulfurization with Raney nickel furnished protected nicotianamine and final deprotection with TFA and purification on Dowex 50W x 8 resin afforded nicotianamine (**4**); $[\alpha]_D^{20}$

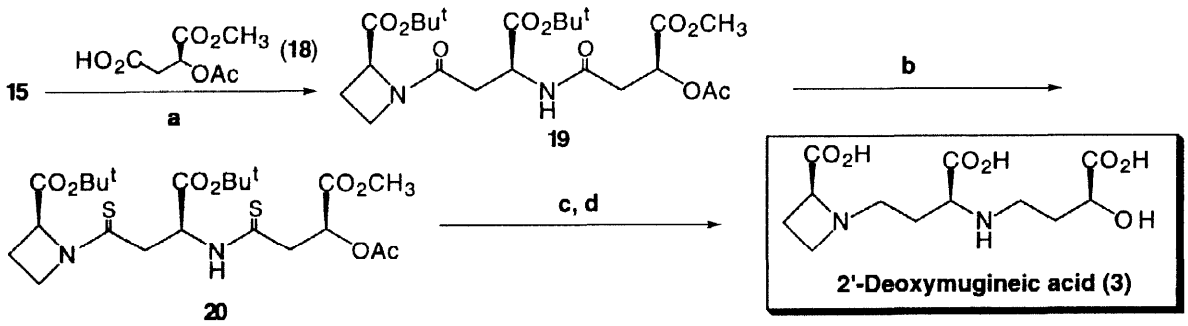
-47.4° (c 0.5,H_2O) [lit.[6a]:$[\alpha]_D^{20}$ -45°(c 0.2,H_2O), lit.[2]: $[\alpha]_D^{28.5}$ -43.4° (c 0.37, H_2O), lit.[12]: $[\alpha]_D^{24}$-51.7°(c 0.37, H_2O)]. The ^1H NMR and ^{13}C NMR data were in full agreement with the reported values. (25.5% overall yield in 7 steps)



Scheme 3

a) i) H_2, Pd/C, EtOAc. ii) **14**, HBTU, *N*-Ethylmorpholine, MeCN, 69%. b) i) H_2, Pd/C, EtOAc.ii) **11**, HBTU, *N*-Ethylmorpholine, MeCN, 82%. c) Lawesson's reagent, C_6H_6, 80°C, 5h, 74%. d) Raney nickel (W-2), EtOH, 50° C, 3 h, 61%. e) TFA & then Dowex purification, quant.

Synthesis of 2'-deoxymugineic acid was realised according to Scheme 4. The dipeptide **15** was subjected to hydrogenation and coupling with the acid unit **18**[13] gave tripeptide **19**. The tripeptide **19** was converted to the corresponding thioamide by Lawesson's reagent and subsequent desulfurization was achieved with Raney nickel to afford protected 2'-deoxymugineic acid. Finally treatment with TFA and 1% methanolic KOH solution at room temperature followed by chromatography on Dowex 50W x 8 resin gave 2'-deoxymugineic acid (**3**); $[\alpha]_D^{24}$ -72° (c 0.32, H_2O)[lit.[14]: $[\alpha]_D$ -70.5°, lit.[2]: $[\alpha]_D^{24}$ -62.3° (c 0.31, H_2O)]. The spectral data were in agreement with the literature values. (26.5% overall yield in 8 steps)



Scheme 4

a) i) H_2, Pd/C, EtOAc. ii) **18**, HBTU, *N*-Ethylmorpholine, MeCN, 85%. b) Lawesson's reagent, C_6H_6, 80°C 5h , 78%. c) Raney nickel (W-2), EtOH, rt-90 min, 61%. d) TFA, rt, 3h; 1% KOH, MeOH, rt, 12h & then Dowex purification, 95%.

In conclusion, we have developed a novel, simple and straightforward method for the synthesis of phytosiderophores and demonstrated by synthesizing three of the phytosiderophore family members. This method will find a greater application for the preparation of analogous phytosiderophores.

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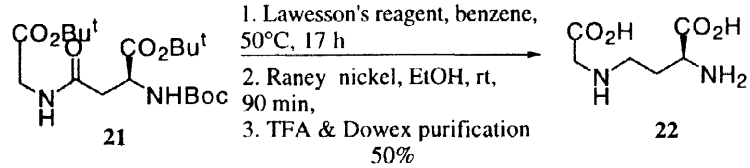
15. While preparing the nicotianamine model compound **22** initially we protected the -COOH groups with benzyl ester and failed to get desired product during the course of desulfurization step with Raney nickel. Subsequently *tert* - butyl ester group was chosen.



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