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A short practical synthesis of 2′-deoxymugineic acid

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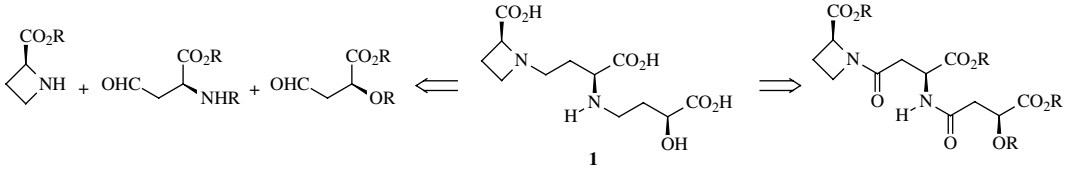
Abstract—A short and practical synthesis of 2′-deoxymugineic acid (DMA) has been developed via reductive alkylation with the aldehyde intermediates. No protection of azetidine-2-carboxylic acid was required and the presence of free carboxylic acid function facilitated purification by simple acid and base extractions. Furthermore, the intermediates were conveniently purified by HPLC due to the presence of chromophoric benzyl ester protecting group(s). Hydrogenolysis of the benzyl protecting groups in the final step furnished DMA in overall good yield.

1. Introduction

2′-Deoxymugineic acid (DMA) is an important phytosiderophore. It is isolated from the roots of graminaceous plants, for example, barley, oats, rice, wheat, etc. It is produced when these plants are kept under iron-deficient conditions. Its main function is to chelate Fe^{III} from the soil and assist in its transportation in the plants.[1]

The importance of DMA in plant physiology has led several groups to develop its synthesis.[2] DMA (**1**) molecule contains two reduced peptide bonds and one α-hydroxy acid. As shown in Scheme 1, it can be assembled from three appropriately functionalized building blocks. There are mainly two strategies for its synthesis: (1) reductive alkylation with the protected aldehydes,[3–6] and recently, (2) reduction of the amide bond via conversion to thioamide and subsequent desulfurization with Raney-nickel.[7,8] Reductive alkylation has been carried out with a protected carboxylate aldehyde[3–5] or with a masked carboxylate functionality, such as *p*-methoxyphenyl group, which is then oxidized to afford a carboxylic acid.[6]

DMA is a polar molecule and has to be purified using H^+ ion-exchange chromatography, because it does not contain any chromophore to allow purification by reversed phase HPLC. In this communication, we report a short and practical synthesis of DMA via reductive alkylation. The important aspect of the synthesis is the choice of the protecting groups that permitted purification of the intermediates by reversed phase HPLC. Furthermore, we would like to point out that the use of a base in the final step of DMA synthesis should be avoided because it leads to the formation of lactam,



Scheme 1.

Keywords: DMA; 2′-Deoxymugineic acid; Reductive alkylation; Reduced peptide bond.
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which is difficult to separate. In earlier reports, molecular ion peak for lactam has been presumed to be the fragment ion peak for DMA $[M+H-H_2O]^+$.[8]

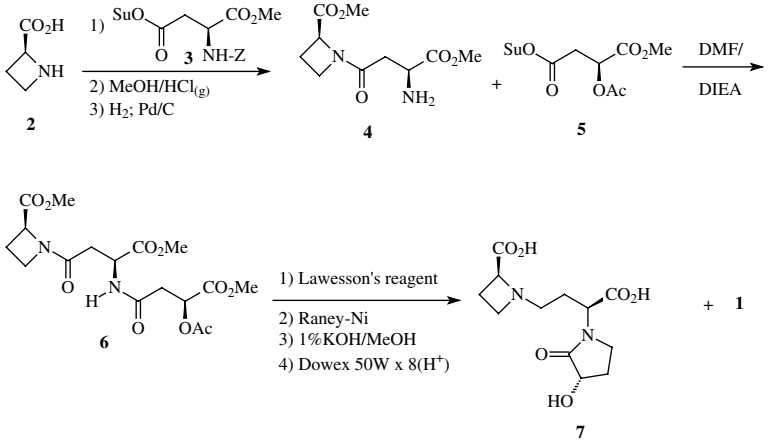
2. Results and discussion

Synthesis of DMA appeared to be rather straightforward using either of the above-described approaches. In our first attempt, we followed the strategy of thioamide reduction,[7] because the preparation of the building blocks was convenient. Besides, protection of the carboxylic acid groups as methyl esters further improved the overall synthesis.

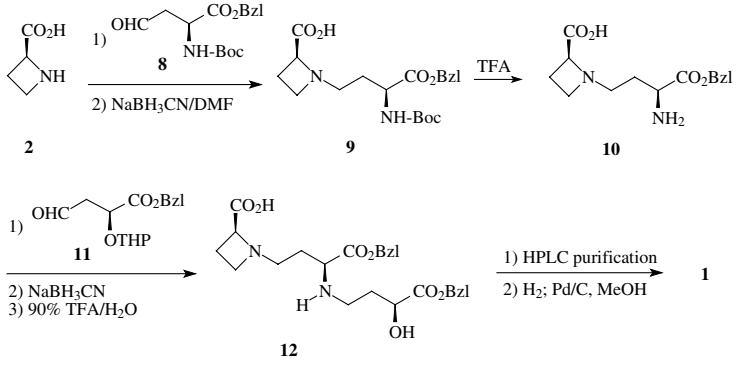
As shown in Scheme 2, azetidine-2-carboxylic acid (**2**) was reacted with Z-Asp(OSu)-OMe (**3**), which after esterification with $MeOH/HCl_{(g)}$ and hydrogenation afforded the dipeptide **4** in 85% yield. Use of OSu ester **3** eliminated the need for protection of the carboxylic acid function of **2**, which has been synthesized in three steps.[9] Treatment of the dipeptide **4** with the protected malic acid OSu ester **5** in the presence of diisopropylethylamine (DIEA) gave the tripeptide **6** in good yield (83%).[10] Reduction of the amide bond was accomplished in two steps: thioamidation with Lawesson's reagent[11] and hydrogenolysis with Raney-nickel.[12] The final step involved the base-mediated hydrolysis of the ester groups. The crude product was purified by using Dowex 50 W × 8 (H^+) ion-exchange resin with 1 N aqueous ammonia as the eluting agent as described earlier.[7,13] However, MS analysis revealed significant contamination from the lactam **7**, which perhaps formed during the base-mediated hydrolysis of the ester functions in contrast to earlier reports.[4,7,8] Base-catalyzed lactam formation is similar to aspartimide formation in peptides containing Asp-Gly motif. The problem is minimized by employing a bulky protecting group group, such as *t*-butyl or using a milder base.[14] Alternatively, the secondary amine function could be protected with a suitable protecting group and should be cleaved only in the last step after deprotection of the carboxy function of malic acid moiety.[3]

Therefore, another strategy was designed, which avoided the use of alkaline reagents during synthesis as well as purification. Furthermore, the protecting groups were chosen in such a way as to allow monitoring and purification by HPLC.

As shown in Scheme 3, reductive amination of Boc-Asp(H)-OBzl (**8**) with the unprotected azetidine-2-carboxylic acid (**2**) afforded **9** in 51% yield.[15,16] The reaction was conducted in 1% AcOH/DMF as solvent and utilized solid $NaBH_3CN$ as the reducing agent. Use of unprotected amino acid **2** was based on two reasons: (1) reductive alkylation can be performed in DMF containing 1% AcOH;[17] thereby, unprotected –COOH



Scheme 2.



Scheme 3.

group in **2** was not considered a hindrance, and (2) the presence of free carboxylic acid would allow isolation of the intermediate(s) by simple acid base extractions. Cleavage of the Boc protecting group with TFA/DCM (1:1) afforded **10** in quantitative yield.[18] Reductive alkylation of **10** with THP protected malic acid half aldehyde **11** in 1% AcOH/DMF gave THP/benzyl protected DMA in 52% yield. Unreacted acid **10** was quantitatively recovered from the reaction mixture by extraction with 5% aqueous sodium carbonate solution, followed by acidification with HCl. The crude THP/benzyl protected DMA was treated with 90% TFA/H_2O at ambient temperature for 30 min, which afforded dibenzyl protected DMA **12** in 96% yield. Partially protected DMA **12** was purified by reversed phase HPLC to 95% purity using standard 0.1% TFA/H_2O/MeCN buffers in 48% isolated yield.[19] Hydrogenolysis of the benzyl protecting groups using 10% Pd/C and H_2 gas in MeOH at 60 psi occurred quantitatively and without any lactam formation. Removal of the solvent and crystallization from H_2O/EtOH afforded DMA as a white solid in >12% overall yield, which exhibited same physical and spectrometric characteristics as the reference DMA sample.

The aldehyde **11** was prepared from the commercially available (*S*)-(−)-α-hydroxy-γ-butyrolactone via protection of the hydroxyl function with DHP, hydrolysis of the lactone with aqueous KOH, protection of the carboxylic acid function with benzyl bromide, and Swern oxidation of the primary alcohol.[3] We also tried TBS protecting group for the α-hydroxyl group of γ-butyrolactone.[5] However, TBS group was less stable to alkaline conditions, which were used in the next step to hydrolyze the lactone.

In summary, a short and practical synthesis of DMA was developed. The new synthesis has several advantages. For example, synthesis involves fewer steps than reported in literature. The reactions are easy to monitor by HPLC. The intermediates could be purified simply by acid and base extractions or by reversed phase HPLC. Overall yield using above strategy was >12%.

Supplementary data

Mass spectrometric analysis of DMA samples obtained from two different methods is available. The supplementary data is available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.030.

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16. Compound **9**. ^{1}H NMR (DMSO-d^6): 7.52–7.28 (m, 5H), 5.23–5.01 (m, 2H), 4.80–4.69 (m, 1H), 4.11–4.04 (m, 1H), 3.80–3.60 (m, 2H), 3.20–3.11 (m, 1H), 3.05–2.95 (m, 1H), 2.50–2.41 (m, 1H), 2.38–2.26 (m, 1H), 2.00–1.85 (m, 1H), 1.85–1.72 (m, 1H), 1.46 (s, 9H).
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18. Compound **10**. ^{1}H NMR (DMSO-d^6): 7.52–7.31(m, 5H), 5.25 (s, 2H), 4.79–4.64 (m, 1H), 4.24–4.01 (m, 1H), 3.81–3.72 (m, 1H), 3.63–3.52 (m, 1H), 3.30–3.20 (m, 1H), 3.16–3.04 (m, 1H), 2.50–2.42 (m, 1H), 2.41–2.36 (m, 1H), 2.17–2.04 (m, 1H), 2.01–1.93 (m, 1H).
19. Compound **12**. ^{1}H NMR (DMSO-d^6): 7.40–7.30 (m, 10H), 5.42–5.33 (m, 1H), 5.15–5.05 (m, 4H), 4.89–4.85 (m, 1H), 4.75–4.68 (m, 1H), 4.29–4.24 (m, 1H), 4.18–4.10 (m, 1H), 3.35–3.30 (m, 1H), 3.30–3.21 (m, 1H), 2.74–2.65 (m, 1H), 2.30–2.22 (m, 2H), 2.10–2.04 (m, 1H), 2.00–1.95 (m, 1H), 1.85–1.75 (m, 2H), 1.67–1.62 (m, 1H).