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Total Synthesis of Matlystatin A

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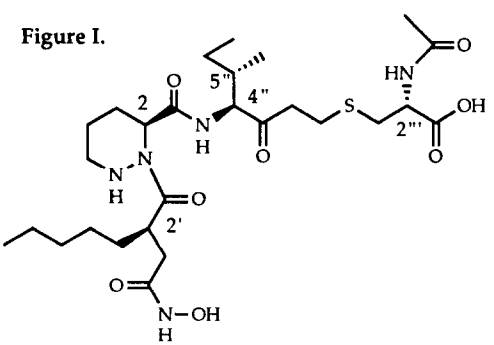
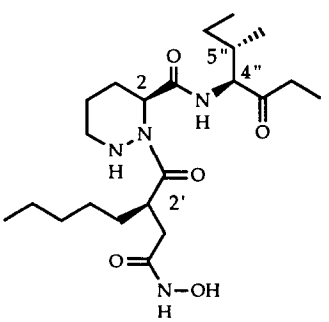
Abstract: Of the five congeners in the matlystatin series, matlystatin A (**1**) is the most potent inhibitor of type IV collagenases. The total synthesis of **1** was accomplished, and the absolute configuration was unambiguously determined as shown in figure I.

Inhibitors of matrix metalloproteinases have attracted much attention for their ability to block tumor cell invasion and metastasis[1]. For example SC-44463, a selective type IV collagenase inhibitor synthesized by the Searle group, inhibits the develop of lung metastasis by B16F10 melanoma cells injected into C57BL mice[2]. Recently BB-94, a matrix metalloproteinase inhibitor discovered by British Biotechnology, dose dependently prolonged the survival of mice bearing HU xenografts[3]. It is thought that inhibitors such as these interrupt the degradation of basement membranes, a requisite process for tumor metastasis.

Figure I.



Matlystatin A
1

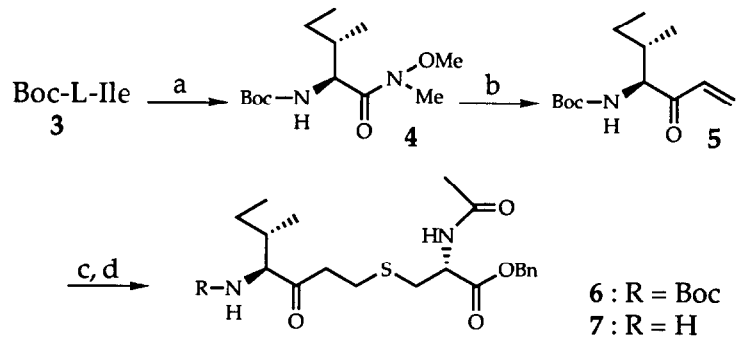


Matlystatin B
2

Matlystatins inhibit the action of type IV collagenases, and were first isolated from *Actinomadura atramentaria*[4]. Matlystatins contain a centrally located piperazic acid unit and a peripherally located hydroxamic acid, which is thought to bind to the zinc atom at the active site of type IV collagenases, thereby inhibiting the enzyme.

In connection with our interests in the biological activities and the novel structures of matlystatins, we planned total syntheses of matlystatin A (**1**) and B (**2**). In the previous paper, we reported the total synthesis of matlystatin B and the relationships between stereochemistry and inhibitory activity[5]. However, the absolute configuration of matlystatin A, the most potent type IV collagenase inhibitor of the matlystatin series, remained to be determined. In this letter we wish to describe the first total synthesis of matlystatin A and the determination of its absolute configuration.

Amine **7** and carboxylic acid **8** were employed as key intermediates in the synthesis of matlystatin A. We described the preparation of the carboxylic acid **8** in our previous paper[5]. The amine **7** was prepared along the route described in scheme I.

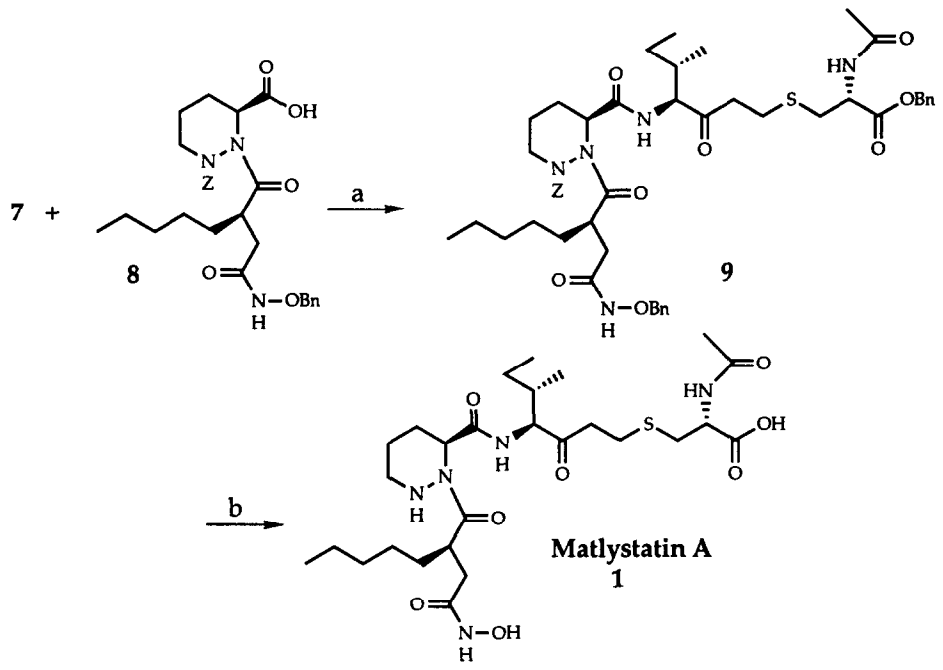


Scheme I Reagents and conditions
(a) $MeN^{+}H_2(OMe)Cl^{-}$, $^{i}Pr_2NEt$, DCC, DMAP, CH_2Cl_2, 0°C, 82% (b) vinylmagnesium bromide, THF, -15°C - r.t., 36% (c.y. 74%) (c) *N*-Ac-L-Cys, pyridine, DMF, r.t. (d) Et_2O solution of phenyldiazomethane, THF, r.t. 34% in 2 steps

Boc-L-Ile (**3**) in dichloromethane was treated with *N,O*-dimethylhydroxylamine hydrochloride and DCC in the presence of $^{i}Pr_2NEt$ and DMAP to give amide **4** in 81% yield[6]. Alkylation of **4** with vinyl magnesium bromide by the method of Weinreb lead to the desired vinyl ketone **5** in 36% yield (74% based on **4** consumed)[7]. The next step, a Michael addition, was accomplished by directly adding *N*-Ac-L-Cys to the THF solution containing **5** and an equimolar amount of Et_3N. To prevent racemization via the oxazolone intermediate, the adduct was esterified with phenyldiazomethane to give benzyl ester **6** in 34% overall yield from **5**[9].

Segments **7** and **8** were coupled as shown in scheme II. The carboxylic acid **8** and amine **7**, prepared by removing the Boc protecting group from **6** by acid hydrolysis, were condensed using diethyl phosphorocyanidate (DEPC) and Et_3N to afford protected matlystatin A (**9**) in 93% yield[8,9]. Final hydrogenation step was carried out using previously prepared Pd-black as a catalyst. After work-up the residue was purified on a preparative HPLC column (Waters Radial-Pak 8NVC18, 70% MeOH-0.2% ($^{v}/_{v}$) Et_3N H_3PO_4 buffer pH 3.3). After removal of MeOH under reduced pressure, matlystatin A (**1**) was obtained by desalting on an ion exchange resin

Diaion HP-20 (Mitsubishi Chemical Industries Ltd., washed with 1N-HCl to remove Et_3N, then with H_2O, and eluted with 50% acetone) to give matlystatin A (**1**) in 49% yield[9].



Scheme II Reagents and conditions
(a) **6**, 4N HCl-1,4-dioxane, r.t. then **8** , DEPC, Et_3N, DMF, 0°C~r.t.,quant.
(b) Pd-black, MeOH, r.t., 49%

The spectral properties (^{1}H-NMR, ^{13}C-NMR, IR, MS, $[\alpha]_D$) of synthetic matlystatin A (**1**) and natural matlystatin A were identical. Thus, the absolute configuration of matlystatin A was unambiguously determined to be 2*S*, 2'*R*, 4"*S*, 5"*S*, 2"'*R* as shown in figure I.

Acknowledgement

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References and notes

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9. Spectral properties of key intermediates (**6**, **9**) and synthetic matlystatin A (**1**) are as follows :
compound **6**: white crystaline solid, mp 91~92°C, IR (film) 3325, 2967, 1734, 1719, 1684, 1648 cm^{-1}, ^{1}H-NMR (400M Hz, $CDCl_3$) δ 0.88 (3H, t, J=7.3 Hz), 0.97 (3H, d, J=6.8 Hz), 1.07, 1.28 each (1H, m), 1.44 (9H, s), 1.86 (1H, m) 2.07 (3H,s), 2.61-2.81 (4H, complex), 3.02 (2H, d, J=4.6 Hz), 4.22 (1H, dd, J=8.5, 4.5 Hz) 4.89 (1H, dt, J= 7.5, 4.6 Hz), 5.04 (1H, br d, J=8.4 Hz), 5.19 (2H, s), 6.56 (1H, br d, J=7.5 Hz), 7.27-7.43 (5H, complex), Anal. Calcd for $C_{25}H_{38}N_2O_6S$: C, 60.70; H, 7.74; N, 5.66; S, 6.48. Found: C, 60.83; H, 7.80; N, 5.60; S, 6.37., $[\alpha]_D^{26}$= +29.0° (c: 1.0, $CHCl_3$)
compound **9**: colorless oil, IR (film) 3297, 2962, 1741, 1702, 1674 cm^{-1}, ^{1}H-NMR (400M Hz, $CDCl_3$) δ 0.73-0.98 (9H, complex) 1.00-1.73 (12H, complex) 1.81-1.98 (2H, complex) 2.05 (3H, s), 2.10-2.30 (3H, complex), 2.40-2.85 (4H, complex), 2.96 (1H, dd, J=13.7, 3.7 Hz), 3.07 (1H, dd, J=13.7, 5.6 Hz), 3.25, 3.83 each (1H, m), 4.09-4.27 (2H, complex) 4.50 (1H,.m), 4.80, 4.89 each (1H, d, J=11.7 Hz), 4.91 (1H, m), 5.03, 5.11 each (1H, d, J=12.0 Hz), 5.24 (2H, s), 7.20-7.45 (15H, complex), 8.31 (1H, br d, J=7.3 Hz), 9.29 (1H, br s), HRMS (FAB) m/z calcd for $C_{49}H_{66}N_5O_{10}S$ 916.4532 $[M+H]^+$, found 916.4526, $[\alpha]_D^{26}$= -44.3° (C: 1.0, $CHCl_3$)
synthetic matlystatin A (**1**): amorphous powder, IR (film) 3293, 2932, 1718, 1655, 1629, 1537 cm^{-1}, ^{1}H-NMR (360M Hz, CD_3OD) δ 0.88, 0.90 each (3H, t, J=7.0 Hz), 0.94 (3H, d, J=6.8 Hz), 1.09-1.72 (12H, complex), 1.90-2.05 (2H, complex), 2.01 (3H, s), 2.12 (1H, m), 2.16 (1H, dd, J=14.4, 5.6 Hz), 2.38 (1H, dd, J=14.4, 9.5 Hz), 2.74-2.93 (6H, complex), 3.02 (1H, m), 3.03 (1H, dd, J=13.9, 4.7 Hz), 3.98 (1H, m), 4.39 (1H, d, J=6.1 Hz), 4.59 (1H, d, J=7.9, 4.6 Hz), 5.17 (1H, dd, J=5.9, 2.2 Hz), ^{13}C-NMR (360M Hz CD_3OD) δ 209.2, 179.3, 174.4, 173.9, 173.3, 171.5, 64.3, 53.8, 52.0, 42.1, 37.8, 37.0, 36.2, 35.1, 33.8, 33.1, 27.6, 27.0, 25.7, 23.6, 22.5, 22.2, 16.4, 14.4, 11.8, HRMS (FAB) m/z calcd for $C_{27}H_{48}N_5O_8S$ 602.3225 $[M+H]^+$, found 602.3226, $[\alpha]_D^{26}$= -39° (C: 0.57, MeOH)

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