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A fast and efficient method for the preparation of the 5-lipoxygenase inhibitor myxochelin A

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ABSTRACT

Previous studies revealed the natural product myxochelin A to possess potent antitumour activity at non-cytotoxic concentrations. While its antiinvasive properties are possibly due to an inhibition of matrix metalloproteinases, the antileukemic effects of myxochelin A could be traced to an inhibition of human 5-lipoxygenase. These findings make myxochelin A an interesting model compound for pharmacological investigations. Here, we present a concise synthetic route for the preparation of myxochelin A, which only involves three steps.

Introduction

The catechol myxochelin A (**1**) is a widely distributed natural product in bacteria.[1] Originally isolated from the culture broth of the myxobacterium *Angiococcus disciformis*,[2] it was later also described from phylogenetically unrelated microorganisms, namely the actinomycete *Nonomuraea pusilla*[3] and the Chloroflexi bacterium *Herpetosiphon aurantiacus*.[4] Myxochelin A is typically secreted in case of an iron deficiency in order to scavenge this important metal from the environment and deliver it to the cell. Aside from its role as a siderophore, **1** was also shown to be modestly active against Gram-positive bacteria.[2] Quite recently, extended bioactivity testing unveiled its potent antitumor effects.[3,5] Myxochelin A suppresses tumor cell invasion at non-cytotoxic concentrations,[3] which is possibly due to an interference with the proteolytic action of two matrix metalloproteinases, MMP-2 and MMP-9.[6] The catalytic domain of MMPs is known to harbour a divalent zinc cation.[7] Complexation of the latter by the catecholate units of **1** might thus be a possible explanation for the observed inhibitory effects.[6]

The strong antileukemic effects of **1** were traced to an inhibition of human 5-lipoxygenase (5-LO).[5,8] This enzyme has a key role in the conversion of arachidonic acid to leukotrienes. The latter are involved in inflammatory processes,[9] and increasing evidence suggests that they also represent mediators of tumorgenesis.[10–12] The active site of 5-LO features a catalytically important non-heme–iron atom,[13] suggesting that the complexing properties of **1** might again contribute to its bioactivity. The catechol natural product **1** is hence a promising tool compound for the functional interrogation of MMPs and 5-LO. Up to now, only one route for the total synthesis of **1** has been described with an overall yield of 23.7%.[3] Here, we describe a concise and more efficient strategy for the synthesis of this natural product with a total yield exceeding 70%.

Results and discussion

The synthetic strategy involves the coupling of commercially available L-lysine ethyl ester with a protected 2,3-dihydroxybenzoic acid derivative, the subsequent reduction of ester **2** to alcohol **3** and finally the deprotection of the catechol moieties (Scheme 1). 2,3-Dimethoxybenzoic acid was chosen as the starting material for the coupling reaction, since it is commercially available and the dealkylation of methoxy groups employing boron tribromide is reliable. After evaluation of several coupling methods, among them *N*,*N*′-dicyclohexyl-carbodiimide and 1-hydroxybenzotriazole (HOBt), 3-(ethylimino-methyleneamino)-*N*,*N*-dimethylpropan-1-amine and HOBt, isobutyl chloroformate and *N*-methylmorpholine, benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexafluorophosphate (pyBOP) and *N*,*N*-diisopropylethylamine (DIPEA),[14] the activation of the carboxylic acid as phosphonium salt with pyBOP[15] proved to be the best method giving a yield of 85% of ethyl-N^2,N^6-bis(2,3-dimethoxybenzoyl)-L-lysinate (**2**). The subsequent reduction of

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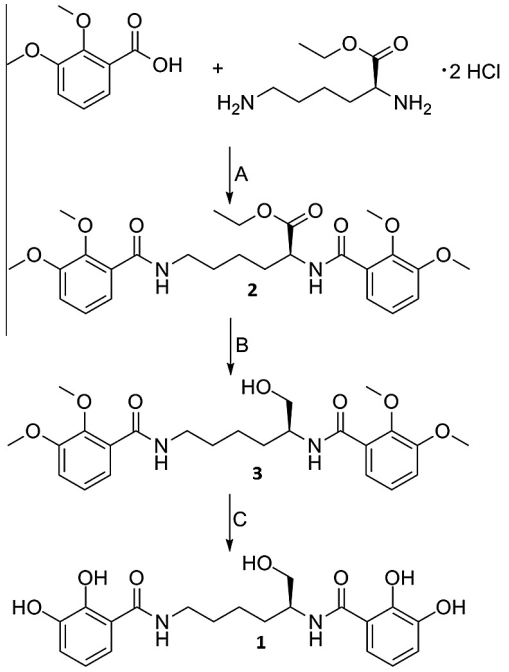

Scheme 1. Reagents and conditions: (A) pyBOP, DIPEA, DMF, rt, 16 h, 85%; (B) $LiBH_4$, THF, EtOH, 4 °C, 15 min → rt, 16 h 88%; (C) BBr_3, DCM, rt, 16 h, 97%.

the ethyl ester to form **3** was carried out with lithium borohydride. Finally, the deprotection of the catechol moieties with 12 equiv of boron tribromide[16] resulted in the formation of **1** in a total yield of 72.5% over three steps. The measured analytical data of the synthesized compound are fully consistent with literature values for **1**.[3]

Conclusion

In this brief Letter, we report an easy method for the preparation of the antileukemic natural product **1**. Using a biomimetic strategy,[1,8] in which the aromatic residues are attached to a lysine moiety prior to the reduction of the central carboxylate group, a step-economical synthesis of **1** has been achieved. In terms of yield, the presented method is more efficient than the procedure, in which the reduction reaction precedes the installation of the aromatic moieties.[3] A facile access to **1** will now certainly foster further research activities in the pharmacological field.

Experimental section

Preparation of ethyl-N^2,N^6-bis(2,3-dimethoxybenzoyl)-L-lysinate (2)

For the preparation of compound **2**, L-lysine ethylester dihydrochloride (2 mmol) was dissolved in 20 ml dry DMF under an argon atmosphere at room temperature. Subsequently, 2,3-dimethoxybenzoic acid (4 mmol), pyBOP (4 mmol) and *N*,*N*-diisopropylethylamine (6 mmol) were added and the solution was stirred at room temperature for 16 h. Afterwards, the reaction solution was poured into 100 ml of ice water. The mixture was exhaustively extracted with ethyl acetate (EtOAc). The organic layers were combined and dried by addition of sodium sulfate. After evaporation of the solvent, the crude product was purified by silica open column chromatography employing a gradient from dichloromethane (DCM)/*n*-hexane 1:1 to DCM to DCM/EtOAc 1:1 (yield: 85%).

Preparation of (*S*)-*N*,*N*′-(6-hydroxyhexane-1,5-diyl)bis(2,3-dimethoxybenzamide) (3)

Compound **3** was prepared by dissolving **2** (1.6 mmol) in 10 ml dry tetrahydrofurane under an argon atmosphere in an ice water bath. Lithium borohydride (1.6 mmol) and dry ethanol (10 ml) were added and the reaction mixture was stirred for 15 min at 4 °C. Afterwards, the solution was allowed to warm to room temperature and stirring was continued for 16 h. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (20 ml). After 15 min of stirring at room temperature, the organic solvents were evaporated under reduced pressure and the aqueous suspension was exhaustively extracted with EtOAc. The organic layers were combined and dried by the addition of sodium sulfate. After evaporation of the solvent, the crude product was purified by C_8-HPLC using 80% aqueous methanol as the mobile phase (yield: 88%).

Preparation of 1

For the dealkylation reaction, **3** (1.5 mmol) was dissolved in dry DCM (10 ml) under an argon atmosphere. Boron tribromide (18 mmol) was added as a 1 m solution in DCM. The reaction mixture was stirred at room temperature for 16 h, afterwards the reaction was stopped by the addition of water (5 ml) and the solvent mixture was evaporated to dryness. The crude product was extracted with methanol and subsequently purified by C_8-HPLC using 60% aqueous methanol as the mobile phase (yield: 97%).

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Supplementary data

Supplementary data (NMR and HR-ESI-MS spectra of all prepared compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.047.

References and notes

1. Silakowski, B.; Kunze, B.; Nordsiek, G.; Blöcker, H.; Höfle, G.; Müller, R. *Eur. J. Biochem.* **2000**, *267*, 6476–6485.
2. Kunze, B.; Bedorf, N.; Kohl, W.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1989**, *42*, 14–17.
3. Miyanaga, S.; Obata, T.; Onaka, H.; Fujita, T.; Saito, N.; Sakurai, H.; Saiki, I.; Furumai, T.; Igarashi, Y. *J. Antibiot.* **2006**, *59*, 698–703.
4. Kiss, H.; Nett, M.; Domin, N.; Martin, K.; Maresca, J. A.; Copeland, A.; Lapidus, A.; Lucas, S.; Berry, K. W.; Glavina Del Rio, T.; Dalin, E.; Tice, H.; Pitluck, S.; Richardson, P.; Bruce, D.; Goodwin, L.; Han, C.; Detter, J. C.; Schmutz, J.; Brettin, T.; Land, M.; Hauser, L.; Kyrpides, N. C.; Ivanova, N.; Göker, M.; Woyke, T.; Klenk, H.; Bryant, D. A. *Stand. Genom. Sci.* **2011**, *5*, 356–370.
5. Schieferdecker, S.; König, S.; Koeberle, A.; Dahse, H. M.; Werz, O.; Nett, M. *J. Nat. Prod.* **2015**, *78*, 335–338.
6. Miyanaga, S.; Sakurai, H.; Saiki, I.; Onaka, H.; Igarashi, Y. *Bioorg. Med. Chem.* **2009**, *17*, 2724–2732.
7. Maskos, K. *Biochimie* **2005**, *87*, 249–263.
8. Korp, J.; König, S.; Schieferdecker, S.; Dahse, H. M.; König, G.; Werz, O.; Nett, M. *ChemBioChem* **2015**, *16*, 2445–2450.
9. Rådmark, O.; Werz, O.; Steinhilber, D.; Samuelsson, B. *Biochim. Biophys. Acta* **2015**, *1851*, 331–339.
10. Rådmark, O.; Samuelsson, B. *J. Intern. Med.* **2010**, *268*, 5–14.
11. Chen, Y.; Hu, Y.; Zhang, H.; Peng, C.; Li, S. *Nat. Genet.* **2009**, *41*, 783–792.
12. Guriec, N.; Le Jossic-Corcos, C.; Simon, B.; Ianotto, J. C.; Tempescul, A.; Dréano, Y.; Salaün, J. P.; Berthou, C.; Corcos, L. *Biochim. Biophys. Acta* **2014**, *1842*, 2096–2105.
13. Ford-Hutchinson, A. W.; Gresser, M.; Young, R. N. *Annu. Rev. Biochem.* **1994**, *63*, 383–417.
14. Han, S. Y.; Kim, Y. A. *Tetrahedron* **2004**, *60*, 2447–2467.
15. Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205–208.
16. Doyagüez, E. G. *Synlett* **2005**, 1636–1637.