Tetrahedron Letters 53 (2012) 4209–4211

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient synthetic method of Psammaplin A

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ARTICLE INFO

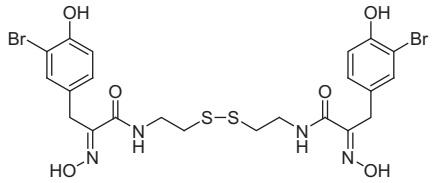
Article history:
Received 4 May 2012
Revised 25 May 2012
Accepted 30 May 2012
Available online 7 June 2012

Keywords:
Total synthesis
Psammaplin A

ABSTRACT

A new concise and efficient synthetic method of Psammaplin A was developed. Psammaplin A was obtained with 50% overall yield in nine steps from *p*-hydroxybenzaldehyde and ethyl acetoacetate via Knoevenagel condensation and direct nitrosation as key steps. This method might be very efficient to construct a quite diverse library of Psammaplin A type analogs.

Psammaplin A was originally isolated independently by three different research groups from the *Psammaplysilla* sponge or unidentified sponges in 1987.[1–3] Psammaplin A has a unique symmetrical structure of bromotyrosine-derived disulfide dimer. Biological activity studies revealed that Psammaplin A has various bioactivities such as antimicrobial activity,[4] cytotoxicity against the leukemia cell-line P388,[1,5] and inhibition of DNA topoisomerase,[6] histone deacetylase,[7] DNA gyrase,[4] farnesyl protein transferase,[8] and leucine aminopeptidase.[8] In addition, Psammaplin A activates PPARγ and induces apoptosis in human breast tumor cells.[9]



1 Psammaplin A

Recently, Shin group, one of our research collaborators, also isolated Psammaplin A from an unidentified sponge collected from the south region of Korea, and confirmed significant cytotoxicity against the leukemia cell-line as reported in previous studies. Their structure–activity relationship (SAR) study with the semi-synthetic derivatives from Psammaplin A revealed that the tetramethoxy analog showed 10 times higher cytoxicity than that of Psammaplin A itself.[10] As one of our research programs for the development of new therapeutics for the treatment of cancer, we needed to develop very concise and efficient synthetic methods of Psammaplin A and its analogs. In this Letter, we present a new efficient and concise synthetic method of Psammaplin A.

Nicolaou group reported a very efficient combinatorial synthetic method of Psammaplin A and its analogs for systematic SAR study as antibacterial agents against methicillin-resistant *Staphylococcus aureus* (MRSA) by modification of Hoshino's[11] synthesis.[12,13] They employed amino acid **2** as the starting material which was converted into α-keto acid **5** via oxazolone **4**. The synthesis of Psammaplin A was completed by the α-oxime formation of **5** using tetrahydropyranoxyamine, followed by the symmetric amide coupling of the resulting α-oxime acid **6** with cystamine (Scheme 1).

Although their synthetic method is very efficient with 6–8 steps, the synthesis starts from or via amino acids that are somewhat limited in diversity because of the limitation of their commercial availability. In addition, the amino group of **3** was removed during the conversion into α-keto acid **5** and then, α-nitrogen moiety of **6** was reintroduced by the formation of oxime, which might be less efficient in respect to atom economics. To improve such shortcomings, we need to find an efficient synthetic method which does not involve amino acids as intermediates, but starts with a more diverse and commercially available resource. As shown in Scheme 2, we planned to introduce the α-oxime moiety directly by α-nitrosation, followed by rearrangement.

First, we needed to prepare **10** as the substrate of nitrosation (Scheme 3). Since the mono-alkylation of active methylene dicarbonyl compounds with alkyl halides usually accompany dialkylated compounds, the purification process of mono-alkylated

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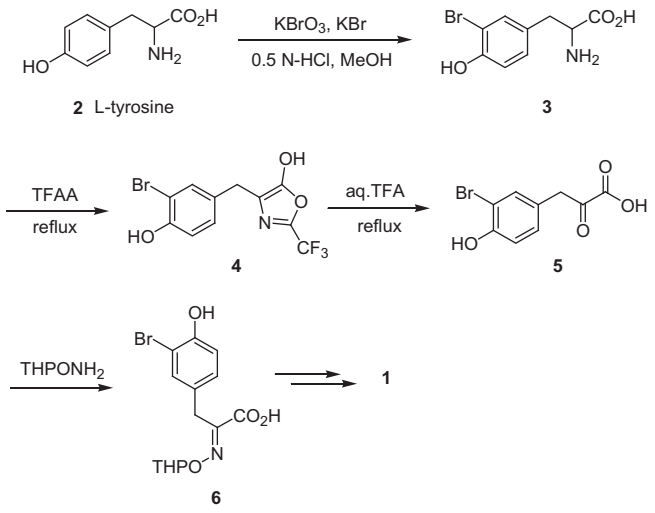
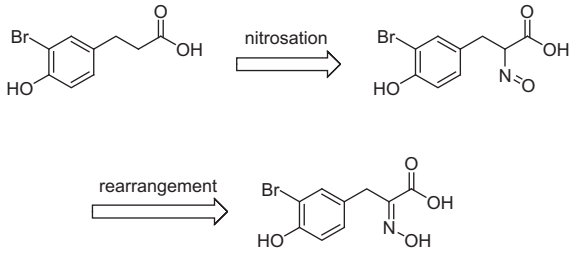
http://dx.doi.org/10.1016/j.tetlet.2012.05.149



Scheme 1. Nicolaou group's synthetic method of Psammaplin A (**1**).

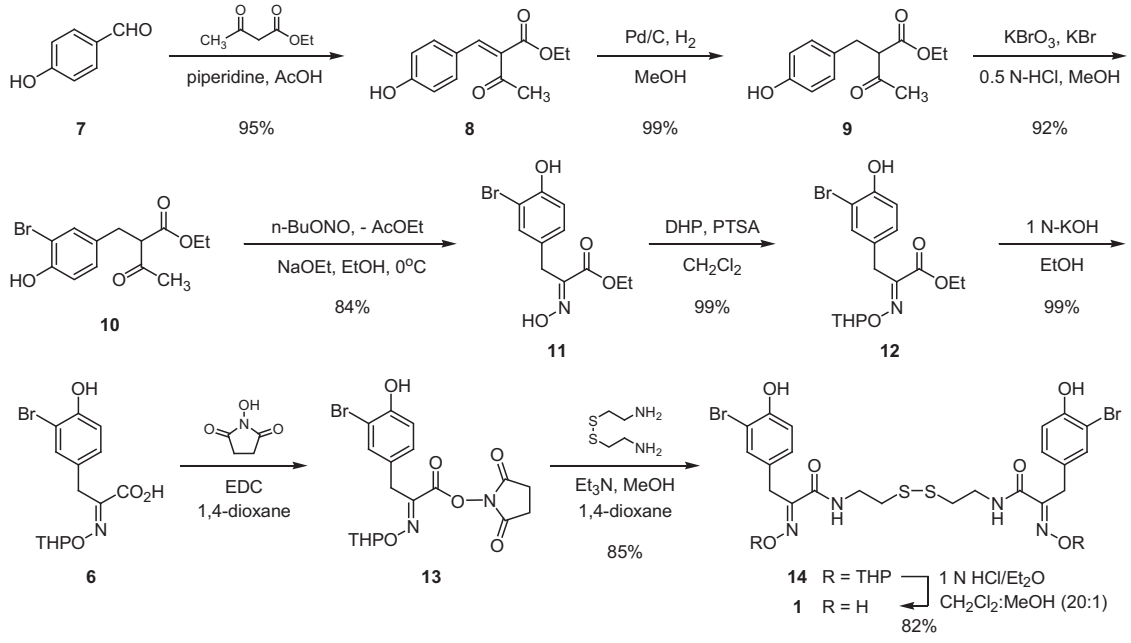


Scheme 2. Synthetic strategy for the key intermediate of α-oxime acid.

compounds from dialkylated ones is sometimes very hard, depending on the alkyl halides. After several trials, we finally chose Knoevenagel condensation, followed by reduction to get the substrate of nitrosation. Initially, Knoevenagel condensation of ethyl acetoacetate with 3-bromo-4-hydroxybenzaldehyde using piperidine in acetic acid successfully gave a 3-bromo-substituted analog of **8**. However 3-bromo moiety was partially removed during the reduction of the unsaturated double bond by catalytic hydrogenation. Therefore we changed our synthetic route via introducing the 3-bromo group after the reduction step. Knovenagel condensation of ethyl acetoacetate with 4-hydroxybenzaldehyde (**7**) using piperidine in acetic acid successfully gave α,β-unsaturated ester **8** (95%).

Compound **8** was selectively reduced to **9** by the catalytic hydrogenation using Pd/C and H_2 in methanol (99%). Selective bromination could be accomplished by treatment of **9** with $KBrO_3$ and KBr under 0.5 M-HCl in methanol to provide **10** (92%). Next, a direct nitrosation of **10** was performed by modification of Barry's conditions.[14,15] The treatment of *n*-butylnitrite to **10** in the presence of sodium ethoxide base under EtOH solvent at 0 °C afforded the corresponding α-NO substituted analog of **10** as an intermediate. After α-nitrosation, immediately, the release of ethyl acetate via fragmentation induced by addition of ethoxide anion to the acetyl group, followed by the double bond conjugation of α-NO group via rearrangement afforded the key intermediate (*E*)-α-oximino ester **11** in a high chemical yield (84%).[16] The protection of the oxime hydroxyl group of **11** using dihydropyran (DHP) in the presence of catalytic amount of *p*-toluenesulfonic acid (PTSA) was performed. Interestingly, we could get only oxime hydroxyl group protected product **12**, instead of both phenolic hydroxyl and oxime hydroxyl groups protected one. The thin layer chromatographic monitoring revealed that both protected compounds were initially formed, but gradually returned to mono-protected product **12** (99%), which might be due to the bulky bromide group adjacent to the phenolic hydroxyl group. The removal of THP of phenolic hydroxyl group could be clearly completed by addition of a drop of methanol. The ethyl ester of **12** was hydrolyzed to the corresponding acid **6** with 1 M-KOH in ethanol (99%). Activation of **6** by coupling with *N*-hydroxysuccinimide using EDC in CH_2Cl_2, followed by addition of cystamine afforded **14** (85% from **12**). Finally, the deprotection of THP of **14** under methanolic hydrochloride solution afforded Psammaplin A (82%). Spectral data of the synthetic product were identical with those reported in the literature.[1–3]

In conclusion, a concise and efficient synthetic method of Psammaplin A was developed from ethyl acetoacetate via Knovenagel condensation and direct nitrosation as key steps (50% yield



Scheme 3. Total synthesis of Psammaplin A.

in nine steps). Since the newly developed method can use ethyl acetoacetate and various commercially available aldehydes or alkyl halides as starting materials, it might be a very efficient method to construct a more diverse library of Psammaplin A type analogs. The preparation of Psammaplin A analogs by our new synthetic method and the systematic structure–activity relationship studies on cytotoxicity are now under investigation.

Acknowledgments

This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government (MEST) (NRF-C1ABA001-2010-0020428) and a Grant of the Korea Healthcare technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A092006).

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