Bioorganic & Medicinal Chemistry Letters 24 (2014) 2415–2419

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and biological evaluation of (+)-neopeltolide analogues: Importance of the oxazole-containing side chain

Haruhiko Fuwa *, Takuma Noguchi, Masato Kawakami, Makoto Sasaki

Graduate School of Life Sciences, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan

ARTICLE INFO

Article history:
Received 18 March 2014
Revised 8 April 2014
Accepted 9 April 2014
Available online 18 April 2014

Keywords:
Marine natural products
Macrolides
Antiproliferative activity
Structure–activity relationships
Suzuki–Miyaura coupling

ABSTRACT

We describe the synthesis and biological evaluation of (+)-neopeltolide analogues with structural modifications in the oxazole-containing side chain. Evaluation of the antiproliferative activity of newly synthesized analogues against A549 human lung adenocarcinoma cells and PANC-1 human pancreatic carcinoma cells have shown that the C19–C20 and C26–C27 double bonds within the oxazole-containing side chain and the terminal methyl carbamate group are essential for potent activity.

(+)-Neopeltolide (**1**, Fig. 1) is a 14-membered macrolide natural product that was isolated from a sponge of the Neopeltidae family, collected off the coast of Jamaica by Wright and co-workers.[1] The gross structure including the relative configuration of **1** was proposed on the basis of 2D-NMR analyses and NOE correlations. Subsequently, Panek[2] and Scheidt[3] independently reassigned the relative configuration and unambiguously established the complete stereostructure of **1** through their total syntheses. The structure of **1** consists of a 14-membered macrocyclic backbone embedded with a tetrahydropyran ring and an oxazole-containing side chain attached to the tetrahydropyran. The oxazole-containing side chain of **1** is identical to that of a marine macrolide natural product, (+)-leucascandrolide A (**2**), previously reported by D'Ambrosio et al.[4] These structurally related natural products **1** and **2** have been proposed to be the secondary metabolites of symbiotic cyanobacteria.[1]

Wright et al. have shown that **1** is a single-digit nanomolar antiproliferative agent against several cancer cell lines, including the A549 human lung adenocarcinoma, the NCI/ADR-RES ovarian sarcoma, and the P388 murine leukemia.[1] They have also suggested that **1** may be cytostatic rather than cytotoxic to the PANC-1 human pancreatic carcinoma cell line and the DLD-1 colorectal adenocarcinoma cell line. Kozmin and co-workers have reported that **1** specifically binds to the complex III of the mitochondrial electron transport chain and inhibits mitochondrial ATP synthesis.[5]

The structural and biological aspects of **1** have gained significant interests of the synthetic community; more than fifteen total and formal syntheses of **1** have been reported so far.[6] Furthermore, the structure–activity relationships of **1** have been reported from several groups.[7] Maier[6f] and Scheidt[3b] have independently synthesized some diastereomers of **1** to suggest the importance of the stereogenic centers along the macrocyclic backbone. Floreancig and co-workers have shown that structural alteration of the C8–C9 domain is possible without significant loss of potent activity.[6p] Very recently, we have disclosed the results of our detailed study on the stereostructure–activity relationships of the macrocyclic domain.[6t] Specifically, we have found that the axial orientation of the C5 oxazole-containing side chain relative to the 2,6-*cis*-substituted tetrahydropyran ring is imperative for nanomolar activity, and that the C11 and C13 stereogenic centers appear to control the orientation of the C13 *n*-propyl group that is essential for potent activity. Interestingly, the macrocyclic backbone could be rationally truncated while retaining nanomolar antiproliferative activity. The importance of the oxazole-containing side chain has also been demonstrated in previous studies. Scheidt and co-workers reported that replacement of the side chain with a benzoyl or *n*-octanoyl group resulted in greater than 1,000-fold loss of activity.[3b] Maier and co-workers showed that the *Z*-configuration of the C19–C20 double bond and the distance between the macrolactone domain and the oxazole ring were important for potent activity.[6f] The Floreancig group described that replacing the oxazole ring with a furan, benzene or pyridine ring led to approximately 30- to 3000-fold loss of activity against the HCT-116 colorectal carcinoma cell lines.[6p] Collectively, all these studies indicate that the oxazole ring would

* Corresponding author. Tel./fax: +81 22 217 6214.
E-mail address: hfuwa@m.tohoku.ac.jp (H. Fuwa).

http://dx.doi.org/10.1016/j.bmcl.2014.04.031
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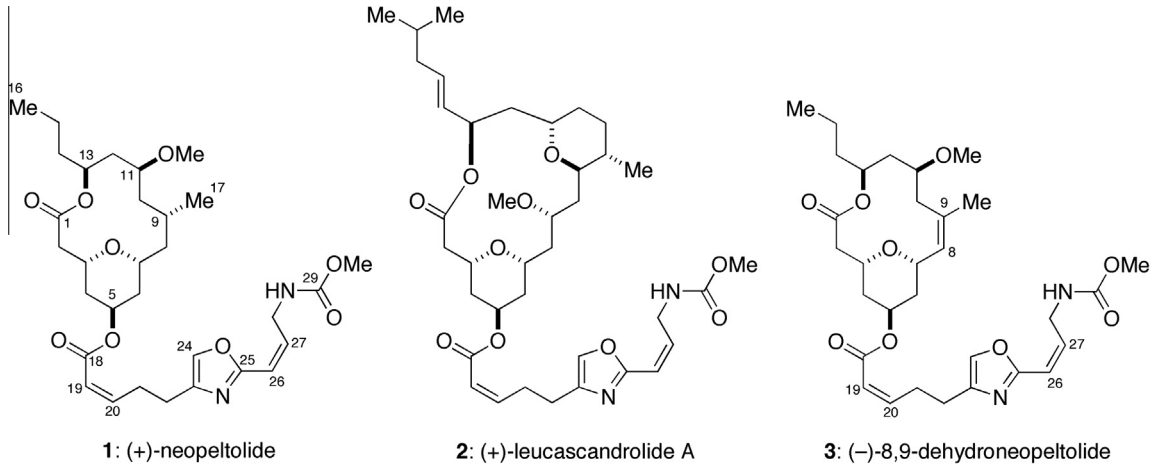


Figure 1. Structures of (+)-neopeltolide (**1**), (+)-leucascandrolide A (**2**), and (−)-8,9-dehydroneopeltolide (**3**).

be indispensable for **1** to show potent antiproliferative activity. However, the importance of the C19–C20 and C26–C27 double bonds and the terminal methyl carbamate group has not been fully addressed.

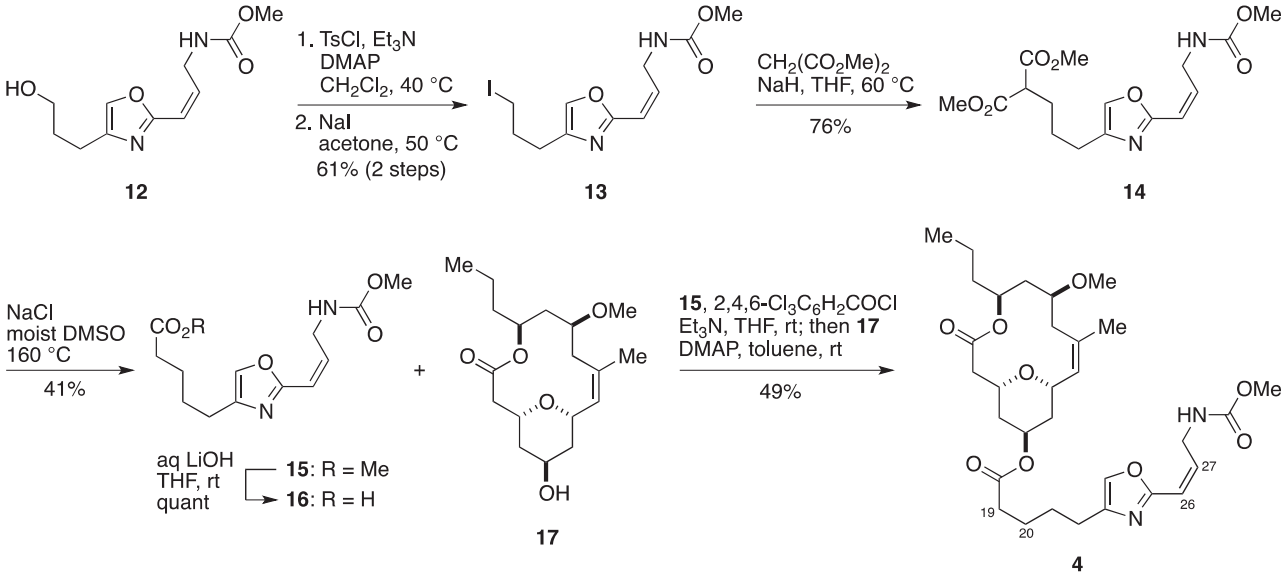
Here we report the synthesis and biological evaluation of neopeltolide analogues to elucidate the structure–activity relationships of the oxazole-containing side chain. Our synthesis of the oxazole-containing side chain via Suzuki–Miyaura coupling[8] facilitated the preparation of a series of side chain analogues. Evaluation of the antiproliferative activity of synthetic analogues against the A549 and PANC-1 cell lines showed that the C19–C20 and C26–C27 double bonds and the terminal methyl carbamate group were essential for low nanomolar activity.

Our previous study has shown that (−)-8,9-dehydroneopeltolide (**3**, Fig. 1) is synthetically more easily available than **1** and that **3** is ca. 3-fold more active than **1** against the A549 cell line.[6t] Accordingly, structural analogues of **3** were synthesized and evaluated in the present study. To address the importance of the C19–C20 and C26–C27 double bonds and the terminal methyl carbamate group, we synthesized a series of side chain analogues **4**–**11** as shown in Schemes 1–4.

The synthesis of the analogue **4**, summarized in Scheme 1, started with tosylation of the known alcohol **12**,[9] followed by displacement with NaI, to give the iodide **13**. Treatment of **13** with dimethyl malonate (NaH, THF, 60 °C) provided the diester **14**, which was decarboxylated under standard conditions[10] to afford the ester **15**. Hydrolysis of the methyl ester of **15** and subsequent esterification[11] of the resultant carboxylic acid **16** with the alcohol **17**[6t] furnished the analogue **4**.[12]

The synthesis of **5** and **6** commenced with hydrogenation of the alcohol **12** (Scheme 2). The resultant alcohol **18** was oxidized under Swern conditions[13] to give the aldehyde **19**, which was homologated using $(CF_3CH_2O)_2P(O)CH_2CO_2Me$[14] to deliver the α,β-unsaturated ester **20** as an inseparable 13:1 mixture of *Z*/*E* isomers. Hydrolysis of **20** gave the α,β-unsaturated carboxylic acid **21**, and subsequent Mitsunobu esterification[15] with the alcohol **22**[6t] afforded the analogue **5**.[12] The minor 19*E* isomer was removed by reverse-phase HPLC purification. Meanwhile, hydrogenation of the double bond of **21** led to the carboxylic acid **23**. Esterification of **23** with the alcohol **17**[6t] under Yamaguchi conditions[11] provided the analogue **6**.[12]

The synthesis of the C19–C20 modified synthetic analogues **7**–**9** started from the known aldehyde **24** (Scheme 3).[6f] Takai methylenation of **24** gave the olefin **25**.[16] Suzuki–Miyaura coupling[8,17] of **25** with a variety of readily accessible alkenyl/aryl iodides **26**,[18] **27**,[19] and **28** provided the coupling products **29**–**31**. Hydrolysis of **29**–**31** followed by Mitsunobu esterification[15] with the alcohol **22**[6f] afforded the analogues **7**–**9**.[12]



Scheme 1. Synthesis of analogue **4**.