Tetrahedron 71 (2015) 5029–5044

Contents lists available at ScienceDirect

Tetrahedron

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

Tetrahedron report number 1084

The apratoxin marine natural products: isolation, structure determination, and asymmetric total synthesis

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ARTICLE INFO

Article history:
Received 30 January 2015
Received in revised form 13 April 2015
Accepted 13 April 2015
Available online 21 May 2015

Keywords:
Asymmetric synthesis
Marine natural products
Polyketide
Depsipeptide
Cytotoxic

Contents

1. Introduction

Apratoxins A–H and apratoxin A sulfoxide (**1**–**9**, Fig. 1) comprise a family of cyclic depsipeptides isolated from the *Lyngbya* species of cyanobacteria.[1–8] The first member of the family to be discovered, apratoxin A (**1**), was isolated in 2001 by Moore, Paul and co-workers'.[1] It was isolated from the marine cyanobacterium *Lyngbya majuscula* from Finger's Reef, Apra Harbor, Guam. Structure determination revealed that apratoxin A (**1**) was composed of discrete polyketide and polypeptide domains, joined via an amide and ester linkage. The polypeptide domain contains three methylated L-amino acid residues (*O*-methyltyrosine, *N*-methyl alanine, *N*-methyl-isoleucine), one L-proline residue, and a modified D-cysteine residue, and the polyketide domain contains four stereogenic centers (C-34, C-35, C-37, and C-39). Apratoxin A exhibited potent in vitro cytotoxicity against KB and LoVo cancer cell lines, with IC_{50} values of 0.52 nM and 0.38 nM, respectively.

2. Isolation and structural determination

Apratoxins B (**2**) and C (**3**) were isolated in 2002 from the same *Lyngbya* sp. of cyanobacterium as apratoxin A, following an

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http://dx.doi.org/10.1016/j.tet.2015.05.047

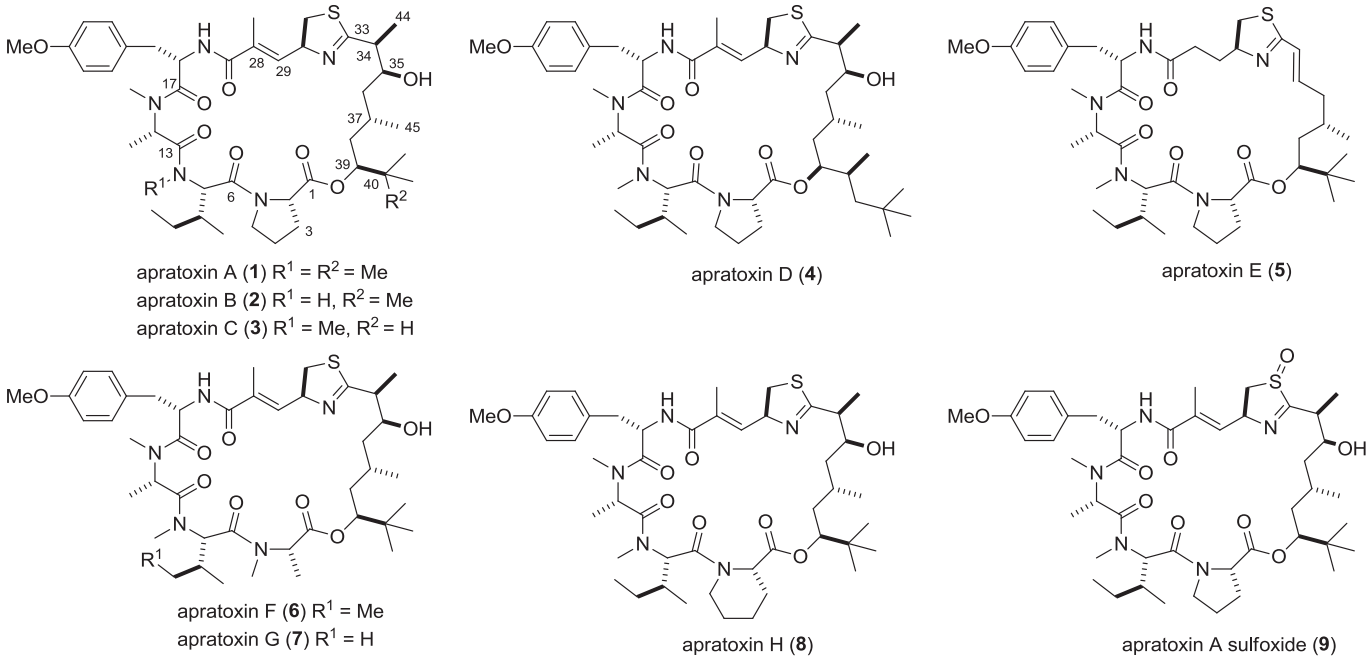

Fig. 1. The apratoxins.

expanded geographical search around the island of Guam and the surrounding Palauan waters.[2] Apratoxin B (**2**) was found in organisms from the same collection site as apratoxin A, whereas apratoxin C (**3**) was produced by specimens collected from Short Dropoff, Palau. Structure determination revealed these new apratoxins to be very similar to apratoxin A, differing only in the degree of methylation; apratoxin B lacks N-methylation of the isoleucine residue, and apratoxin C possesses an isopropyl rather than a *tert*-butyl group at C-39. Apratoxin B displayed potent in vitro cytotoxicity against KB and LoVo cancer cell lines, with IC_{50} values of 21.3 nM and 10.8 nM, respectively. Apratoxin C showed stronger in vitro cytotoxicity than apratoxin B against KB and LoVo cancer cell lines, with IC_{50} values of 1.0 nM and 0.73 nM, respectively.

Apratoxin D (**4**) was isolated in 2008 by Gutiérrez and co-workers' from samples of *Lyngbya majuscula* and *Lyngbya sordida*, off the coast of Papua New Guinea.[3] Interestingly, apratoxin D was found to have the same amino acid sequence as apratoxins A and C, but possessed a new polyketide moiety, 3,7-dihydroxy-2,5,8,10,10-pentamethylundecanoic acid, which was longer than the other apratoxins by an acetate group. Apratoxin D showed potent in vitro cytotoxicity against H-460 human lung cancer cells with an IC_{50} value of 2.6 nM.

Apratoxin E (**5**) was isolated shortly after apratoxin D by Luesch and co-workers' from the cyanobacterium *Lyngbya bouillonii*.[4] Apratoxin E was found to possess an identical polypeptide domain to that of apratoxin A. However, it is unsaturated at the C-34–C-35 bond, and lacks a methyl group at C-34. In addition, the modified cysteine residue is fully saturated at C-28–C-29 and lacks a C-28 methyl group. Apratoxin E exhibited strong cytotoxicity when tested for activity against several human cancer cell lines: HT29 (IC_{50} of 21 nM), HeLa (IC_{50} of 72 nM), and U2OS osteosarcoma cells (IC_{50} of 59 nM).

Apratoxins F (**6**) and G (**7**) were isolated in 2010 by Gerwick and co-workers from samples of *Lyngbya bouillonii* collected from Palmyra Atoll in the Central Pacific.[5] The polyketide moiety of apratoxins F and G was found to match that of apratoxin A. In both apratoxins F and G, the polypeptide portions contain an *N*-methylated alanine in place of the proline residue present in apratoxin A. Apratoxin G had one additional difference, namely, the *N*-methylisoleucine was replaced with *N*-methylvaline. Apratoxins F and G were the first apratoxins isolated to possess significant structural difference in the peptide sequence. Apratoxin F and G displayed potent in vitro cytotoxicity against H-460 lung cancer cells with an IC_{50} of 2 nM and 14 nM, respectively. Additionally, apratoxin F showed potent activity against HCT-116 cell lines (IC_{50} of 36 nM).

Apratoxin H (**8**) and apratoxin A sulfoxide (**9**) were isolated by McPhail and co-workers' in 2013 from the cyanobacterium *Moorea producens*[9] obtained from the Red Sea.[6] Apratoxin H and apratoxin A sulfoxide were found to retain the same polyketide moiety as apratoxin A. Apratoxin H only differed from apratoxin A in that a pipecolic acid residue was present instead of a proline residue. Apratoxin A sulfoxide differed in degree of oxidation in the modified cysteine residue; the sulfur of the thiazoline is oxidized to the sulfoxide. Apratoxin H exhibited potent cytotoxicity towards H-460 lung cancer cells with an IC_{50} value of 3.4 nM, while apratoxin A sulfoxide showed lower cytotoxicity against H-460 lung cancer cells (IC_{50} of 89.9 nM).

The slight structural differences in the apratoxin family hints at mixed biogenetic origins for this class of compounds. This variation is common among cyanobacteria, which often produce more than one member of a certain class of compounds due to relaxed specificity of biosynthetic enzymes during precursor-biosynthesis.[4,10]

3. Total synthesis

3.1. Apratoxin A

Five total syntheses of apratoxin A have been reported: one by Forsyth,[11,12] two by Takahashi and Doi,[7b,13] one by Ma,[7a] and one by Doi.[7d] As outlined in Scheme 1, apratoxin A could logically be disconnected to yield tetrapeptide **10** and the thiazoline containing polyketide **11**. However, one strategy common to all apratoxin A syntheses, based on merging the peptide and polyketide domains, is the early incorporation of the proline residue as the C-39 ester (cf. **13**). This strategy was used in anticipation of a higher yielding amide formation between the isoleucine carboxylate of tripeptide **12a–c** and the proline amine moiety of **13**, in comparison to the coupling between the proline carboxylate of **10** and the hindered C-39 hydroxyl of **11**.[7a,b,d,11–13] Also common to the five syntheses of apratoxin A is the late stage assembly of the thiazoline moiety,