Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Digest paper

An overview of the recent synthetic studies toward penifulvins and other fenestranes

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ARTICLE INFO

Article history:
Received 8 June 2016
Revised 30 June 2016
Accepted 4 July 2016
Available online xxxx

Keywords:
Penifulvin
Fenestrane
Titanocene
Radical cyclization
Asperaculin

ABSTRACT

Complex natural products provide a useful template for the construction of novel molecular scaffolds of biological as well as theoretical interest. In this regard, fenestranes have emerged as a challenging target for organic chemists. The existence of the planarized distortion of the central quaternary carbon in fenestranes away from its standard tetrahedral bond angle makes their synthesis a daunting task. In this review, an attempt has been made to capture the essence of some recent synthetic studies toward these molecules with an emphasis on penifulvins, the first [5.5.5.6]dioxafenestrane.

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http://dx.doi.org/10.1016/j.tetlet.2016.07.011
0040-4039/

Introduction

Origin and molecular structure

The synthesis of natural products with remarkable structural diversity and therapeutic potential[1] enables invention of new synthetic strategies that can be used to make natural products like molecules for modulating various biological targets.[2] In this perspective, terpenes as a family provide an enormous opportunity to synthetic organic chemists to build diverse libraries of new chemical entities. Among the various types of terpenes, a relatively new, but rapidly growing subgroup is composed of fenestranes,[3] a class of compounds having four condensed cycles sharing a central quaternary carbon atom which exhibits planarizing distortion.[4–6] Because of their fascinating structures and their role in the field of planar tetracoordinated carbons (ptCs), fenestranes became a popular target for synthesis and during the past four decades, a large number of compounds of this class were synthesized mainly by utilizing cyclodehydration,[6b] photochemical [2+2],[6b] [3+2] arene–olefin cycloaddition,[7,8] the Pauson–Khand reaction (PKR),[9,10] etc.

The discovery of these sesquiterpene natural products starting from the first naturally occurring molecule, laurenene (**22**)[11] along with the most recent additions of penifulvin A (**1**),[12] its sibling secondary metabolites penifulvin B–E (**2**–**5**)[13] and asperaculin A (**6**),[14] have enriched the family of dioxafenestranes (Fig. 1).

However, planning the synthesis of any molecule of the penifulvin family, and its execution, is extremely challenging. No wonder that examples of such synthetic studies are rare. The purpose of this review is to summarize and highlight the synthesis of penifulvin type molecules along with the synthetic approaches toward them with the hope that this would inspire many more advances in the chemistry and biology of this fascinating class of molecules.

Isolation, characterization and biological profiling

The fall armyworm (*Spodoptera frugiperda*) larvae cause extensive damage to a large variety of crops across the tropical regions of the western hemisphere from the United States to Argentina, with corn in particular being heavily affected.[15] In Florida, the fall armyworm is the most damaging pest of corn and its resistance to pesticides had also been noted warranting the discovery of new pesticides. In 2006, Gloer and co-workers isolated a novel sesquiterpenoid[16] penifulvin A (**1**) and its analogues penifulvin B–E (**2**–**5**) from rice culture[17] of fungal extracts, *Penicillium grisiofulvum*[18] (MYC-1728 = NRRL 35584). From these metabolites, penifulvin A was found to exhibit significant antiinsectan activity in assays against the fall armyworm. All these molecules feature a unique and previously undescribed *c,c,c,c*-[5.5.5.6]dioxafenestranes skeleton in which the 15-carbon framework is composed of five stereogenic centers (except penifulvin E, having six) having among them three vicinal quaternary carbons (except penifulvin D, having four) in addition to both a γ- and δ-lactone connected as an acylal. Penifulvin B–E[19] differed from penifulvin A only in oxidation states at C12, C13, C9 and C10, respectively.

Thereafter, in 2011, another sesquiterpenoid molecule asperaculin A (**6**) was isolated by a research group[14] of Thailand from the mycelial extract of the marine-derived fungus *Aspergillus aculeatus* (CRI323-04). Both penifulvin A and asperaculin A possess dioxa [5.5.5.6]fenestrane core except the transposition of the δ-lactone ring and the presence of an extra hydroxyl group at C9 (in asperaculin A). It didn't exhibit cytotoxic activity (at 50 μg/mL) against HepG2, MOLT-3, A549 and HuCCA-1 cancer cell lines.

Proposed biosynthetic pathways for penifulvin family and asperaculin A

It was hypothesized that the penifulvins might be biogenetically related to the silphinene family of triquinane[20] sesquiterpenoids. The biosynthesis started from farnesyl pyrophosphate (FPP, **7**) (Scheme 1) via carbocationic rearrangement of FPP to the β-caryophyllene[21] cyclobutyl carbocation **8**. Ring expansion of cyclobutane ring gives a five-membered carbocation **9**. Trapping of the carbocation in **9** by the trisubstituted double bond, followed by an 1,3-hydride shift, leads to a tricyclic intermediate **10**. Finally Wagner–Meerwein rearrangement gives rise to silphinene framework **11**. Thereafter, an enzymatic oxidation of the methyl group to the carboxylic acid **12**[22] was followed by oxidative cleavage[16] of cyclopentene ring and subsequent bislactonization to furnish penifulvin A.

According to Mulzer et al.,[7] after oxidative cleavage of the olefin, a dialdehyde intermediate **15** is formed, which cluster to lactol **16** followed by an oxidation giving rise to penifulvin A (Scheme 2).

It has also been suggested that after a site specific enzymatic oxidation of silphinane methyl group to the hydroxylated carboxylic acid **17** followed by oxidative cleavage of the cyclopentene ring and further cyclization/lactonization would give rise to penifulvin B (Scheme 3). The other members of this family are also derived in similar manner.

The proposed biosynthesis of asperaculin A (Scheme 4) starts from a double bond migration (C1/C2 to C2/C3) of the hydroxysilphinene acid (**17**). After that, oxidative cleavage of the cyclopentene ring followed by a sequence of oxidation and lactonization finally gives rise to asperaculin A (**6**).

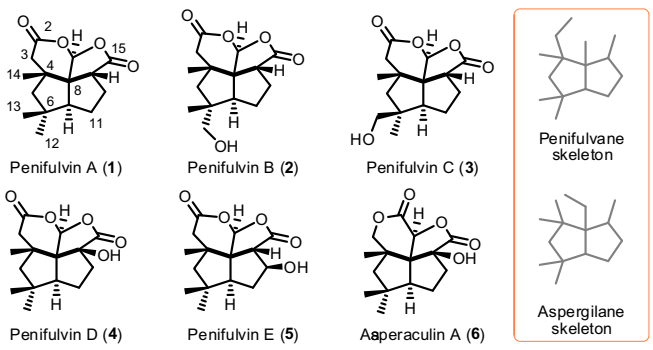
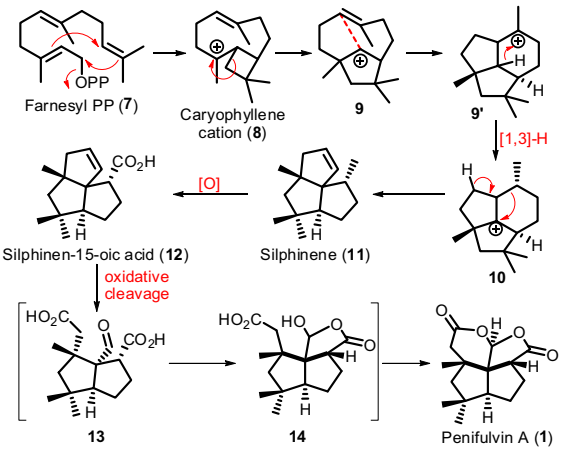


Figure 1. Structures of penifulvins A–E and asperaculin A.



Scheme 1. Proposed biosynthetic pathway of penifulvin A by Gloer et al (Ref. 12).