Tetrahedron Letters 58 (2017) 4025–4038

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Digest paper

Chemical syntheses of the cochliomycins and certain related resorcylic acid lactones

Martin G. Banwell *, Xiang Ma, Benoit Bolte, Yiwen Zhang, Michael Dlugosch

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

ARTICLE INFO

Article history:
Received 19 July 2017
Revised 5 August 2017
Accepted 7 August 2017
Available online 9 August 2017

Keywords:
Resorcylic acid lactones
Synthesis
Natural products

ABSTRACT

The cochliomycins (**7**–**12**) are a group of six resorcylic acid lactones that have recently been isolated from culture broths of marine fungi found in the South China Sea. These natural products have attracted attention as synthetic targets because of (in certain instances) their novel structural features and their capacities to suppress biofouling. This short review summarizes the synthesis of these and some related compounds that have been reported to date, including those developed in the authors' laboratories.

Contents

Introduction

The value of small molecule natural products (SMNPs) as therapeutic agents, as precursors to such agents or as the inspirations for them is well known.[1] Indeed, there are now indications that SMNPs, perhaps especially ones derived from marine environments,[2] are enjoying something of a renaissance not least because of their enormous structural diversity and their occupation of unique parts of chemical space.[3] Among the plethora of different natural product classes, the resorcylic acid lactones (RALs) are notable for the frequency with which they are isolated from fungal sources, their distinctive structural features and their breadth of biological activities.[4] In the following section an overview of the structural variations within the RAL class is provided along with a brief commentary on the source organisms and certain of their biological properties. As a recently discovered and interesting subset of RALs that has not been the subject of any previous reviews, the cochliomycins are then described and a summary of the synthetic work carried out on them follows.

* Corresponding author.
E-mail address: Martin.Banwell@anu.edu.au (M.G. Banwell).

https://doi.org/10.1016/j.tetlet.2017.08.021
0040-4039/

Resorcylic acids lactones (RALs) as a natural product class

The RALs are mycotoxins and the products of a distinctive polyketide biosynthesis that exploits an acetyl CoA starter unit together with malonyl-CoA extenders and involves two fungal polyketide synthases (PKS) that work co-operatively.[4e] Specifically, a non-reducing PKS is coupled with a highly reducing one that enables the assembly of the relevant resorcylic acid core annulated to a 14-membered macrolactone (and wherein most of the structural variation resides). Unsurprisingly perhaps, the final step in the biosynthesis is the macrolactonisation event that releases the substrate from the enzyme complex. Post-PKS-mediated processes such as epoxidation, halogenation and alkylation may then follow so as to provide the fully "decorated" (isolated) metabolite.[4e]

Radiciol (**1**) was the first RAL to be isolated (from *Monosporium nordinii*) and characterised in the 1950s[4] and it has since been obtained from various other fungal strains. In the intervening period numerous other RALs have been identified and these vary in the nature of the substitution pattern on the aromatic ring as well as the location and degree of unsaturation and/or oxygenation within the macrolactone ring. The structures of the RALs hypothemycin (**2**), zearalenone (**3**), pochonin C (**4**), L-783,277 (**5**) and aigialomycin D (**6**) shown in Fig. 1 serve to highlight such degrees of variation.

The discovery of cochliomycins A–F

In papers published in 2011[5] and 2014,[6] Wang and co-workers from the Ocean University of China in Qingdao reported the isolation of cochliomycins A–F (**7**–**12**) (Fig. 2) from the culture broths of *Cochliobolus lunatus* (M351) or *C. lunatus* (TA26-46), fungi associated with the gorgonian *Dichotella gemmacea* or the sea anemone *Palythoa haddoni*, respectively. Both host organisms were collected in the South China Sea. The structures of these RALs were established through the application of the usual battery of spectroscopic methods and the absolute stereochemistries of the last three determined using the CD exciton chirality method in conjunction with TDDFT ECD calculations.[6]

The most striking features of this subset of RALs are the presence of acetonide units within the structures of congeners A and B (**7** and **8**, respectively). Since acetone was not used in the isolation, purification or spectroscopic characterisation of these compounds they must be considered as natural products rather than artefacts. Wang and co-workers also noted[5] that on standing in $CDCl_3$ at ambient temperatures cochliomycin B (**8**) slowly isomerised to congener **7** and so suggesting the latter is the thermodynamically more stable compound. Cochliomycin C (**9**) is the only member of the series lacking a second double bond within the macrocyclic ring. Cochliomycins D (**10**) and E (**11**) are isomeric while congener F (**12**) is not simply a chlorinated derivative of

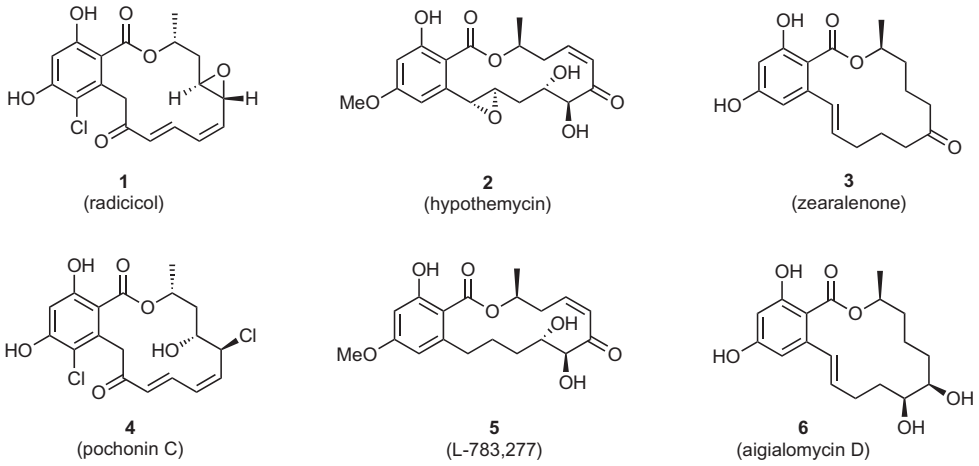

Fig. 1. Examples of the structural variations possible within the RAL class.

Initial biological evaluation of radiciol (**1**) showed it to possess anti-bacterial properties and to act as a mild sedative. However, the later revelation that it acts as a powerful inhibitor of heat shock protein 90 (HSP90) – and thus representing an important lead in the development of oncolytic agents – caused much greater attention to be given to the RALs. In contrast to radiciol (**1**), the *cis*-enone-containing hypothemycin (**2**) has been shown to strongly inhibit the kinase MEK1, while zearalenone (**3**) acts as an estrogen agonist and its hormone-like properties have been shown to promote growth in cattle and sheep. A closely related RAL is now commercially available and employed to alleviate post-menopausal stress in women and as an anabolic cattle-growth stimulant. Pochonin C (**4**), on the other hand, inhibits herpes simplex virus (HSV) replication in a potentially therapeutically useful way while the *cis*-enone L-783,277 (**5**), like congener **2**, inhibits MEK1. Aigialomycin D (**6**), despite the absence of a *cis*-enone moiety, also acts as a kinase inhibitor as well as an anti-malarial agent (the latter property seemingly being unrelated to the former).

one or other of the first two because of the differing configuration at one or other of the hydroxyl-bearing methine carbons. Nor, for the same reasons, can cochliomycin F (**12**) simply be the product of the twofold oxidation of congener **9**.

Related, co-occurring natural products

In the course of structurally characterising the cochliomycins, it was noted[5] that congener C (**9**) is the chlorinated derivative of co-isolated paecilomycin F (**13**) (Fig. 3), a previously reported RAL that displays anti-malarial properties. Other RALs also isolated alongside compounds **7**–**9** were zeaenol (**14**), LL-Z1640-1 (**15**) and LL-Z1640-2 (**16**). During the course of isolating cochliomycins D, E and F (**10**, **11** and **12**, respectively), cochliomycin A (**7**), zeaenol (**14**), LL-Z1640-1 (**15**), LL-Z1640-2 (**16**), its *E*-isomer **17** [(7′*E*)-6′-oxozeaenol], deoxyaigialomycin C (**18**) and aigialomycin B (**19**) were also observed in the mixture of isolates. Clearly certain of these co-isolates are isomeric with the cochliomycins or otherwise