Tetrahedron 69 (2013) 10581–10592

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of diastereomeric, deoxy and ring-expanded sulfone analogues of aigialomycin D

Samuel Z.Y. Ting, Lynton J. Baird, Elyse Dunn, Reem Hanna, Dora Leahy, Ariane Chan, John H. Miller, Paul H. Teesdale-Spittle, Joanne E. Harvey *

Centre for Biodiscovery, Schools of Chemical and Physical Sciences, and Biological Sciences, Victoria University of Wellington, PO Box 600, Wellington 6140, New Zealand

ARTICLE INFO

Article history:
Received 8 August 2013
Received in revised form 24 September 2013
Accepted 14 October 2013
Available online 21 October 2013

Keywords:
Aigialomycin D
Resorcylic acid lactone
Analogue
Methyl orsellinate
Ramberg–Bäcklund
Ring closing metathesis

ABSTRACT

Several analogues of the fungal natural product aigialomycin D (AmD) have been synthesised. These include the stereoisomer 5′*R*,6′*S*-AmD, 2,4-di-deoxyAmD, 1′,2′,7′,8′-tetrahydroAmD and a 15-membered macrocyclic sulfone. Growth inhibitory activities of these compounds against the HL-60 leukaemic cell line were measured. The ring-expanded sulfone and tetrahydro-analogue were found to have similar IC_{50} values to the natural product, whereas the 5′*R*,6′*S*-stereoisomer was inactive. Energy minimisation of AmD and the synthesised analogues resulted in a range of lowest energy conformers, from planar, open arrangements of the macrocycle in AmD and tetrahydroAmD to bent, L-shaped structures for the sulfone. The synthesis of methyl orsellinate was investigated and optimised as part of this work. A stereodivergent route to both enantiomers of the diol fragment from D-ribose was also achieved.

1. Introduction

The resorcylic acid lactones (RALs, Fig. 1), a class of macrocyclic natural products with a variety of biological actions, have gained widespread attention as leads for drug discovery.[1–3] These mycotoxins[4] have a wide range of activities, from antimalarial (aigialomycin D, paecilomycin E)[5,6] to antifouling (cochliomycin A) properties.[7] With respect to biochemical targets, estrogen agonism (zearalenone)[8] and inhibition of the heat-shock protein HSP90 (radicicol, pochonin D)[9–11] are known within the class, yet the majority of the naturally occurring RALs act as protein kinase inhibitors (hypothemycin, L-783,277, LL-Z1640-2, radicicol A and aigialomycin D).[2,3,12]

The privileged benzo-fused 14-membered macrolactone ring of the RALs represents a rich scaffold for structural variation. This is evidenced biosynthetically by the diversity of natural compounds in this class (see Fig. 1), which differ particularly in the degree and positioning of oxidation and unsaturation about the macrolactone ring. The array of bioactivity noted for these compounds indicates the subtle interplay of the functionality and stereochemistry about the ring system. Further structural variation is available through the preparation of analogues, which has been achieved in a de novo synthetic fashion,[13–15] biosynthetically through heterologous gene expression[16] and by semisynthesis.[17] Notable examples of synthetic analogues include cycloproparadicicol and related species,[13a] pochonin-based macrolactams,[13b,c] oxime derivatives of radicicol,[9,13d] deoxygenated L-783,277 variants,[13e] and alkene-[13f,g] and *O*-modified analogues of the RALs.[2,14]

Through these and other studies, an understanding of the structure–activity relationships for these compounds is beginning to be realised. For instance, the potent kinase inhibitors among this class all have a *Z*-enone moiety at C7′–C8′.[3] In contrast, the C7′–C8′ '*trans*'-configured species radicicol (with its *trans*-epoxide) and pochonin D (with an *E*-alkene) behave as HSP90 inhibitors, binding competitively at the ATP-binding site.[2,18] Among the RALs, aigialomycin D (AmD) seems to be an outlier, in that it has the C7′–C8′ *E*-alkene, is a moderate kinase inhibitor, but does not inhibit HSP90.[13a,14a] Aigialomycin D was originally isolated from a marine mangrove fungus (*Aigialus parvus*)[5] and has subsequently been found in two further fungus species.[6,19] It displays moderate growth inhibitory activity against the human epidermoid carcinoma (KB) and breast cancer (BC-1) cell lines and interacts with kinase targets (CDK1, CDK5, GSK3). Its unusual properties and synthetically tractable structure make it a useful starting point for

---

* Corresponding author. Tel.: +64 4 4635956; fax: +64 4 4635237; e-mail address: Joanne.Harvey@vuw.ac.nz (J.E. Harvey).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.10.042

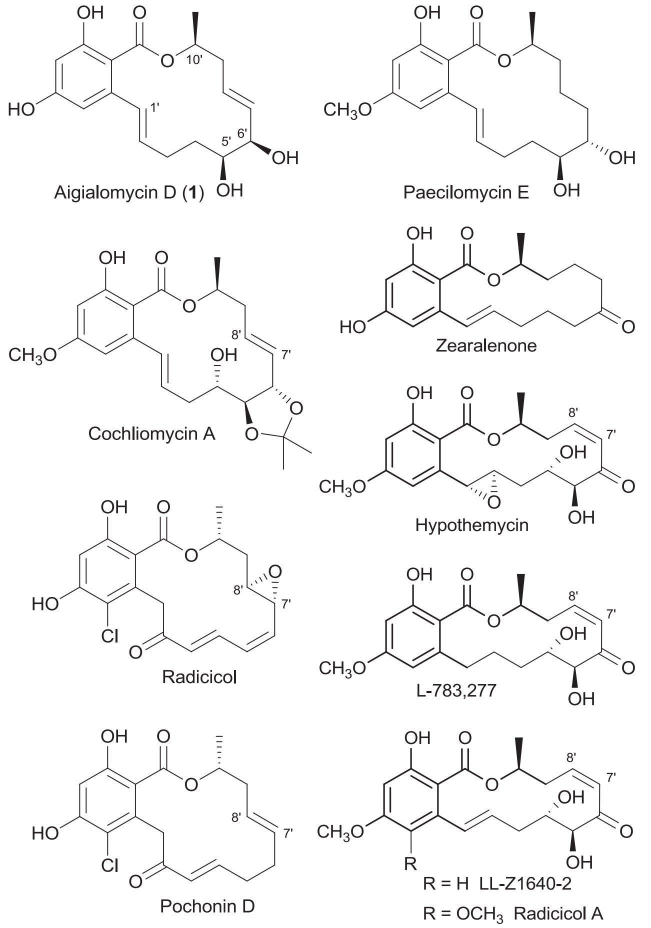


Fig. 1. Representative naturally occurring RALs.

novel analogue synthesis. Preparation of new analogues will shed more light on structural features of the RALs required for therapeutic applications.

To this end, we chose to pursue analogues of aigialomycin D differing from the natural material in the stereochemistry at the diol (C5′ and C6′) (analogue **2**) and methyl (C10′) (analogue **3**) substituents, in the degree of unsaturation on the macrocyclic ring (analogue **4**) and in the oxygenation of the aromatic ring (analogue **5**) (Fig. 2). The RAL ring system embodied by AmD is synthetically accessible by numerous diverse routes.[13,14a,20–22] Our total synthesis of AmD[20] invoked a combination of ring-closing metathesis and Ramberg–Bäcklund reactions.[23,24] This strategy prevents the undesired cyclohexene formation that has been observed if metathesis at C7′–C8′ is performed in the presence of the internal C1′–C2′ alkene.[14a,22a,25] A 15-membered sulfone-containing macrolactone is the penultimate intermediate in the synthetic strategy, and its deprotection would afford a novel analogue that is uniquely accessible through this methodology. The sulfone-containing analogue **6**, therefore, was also pursued in this work.

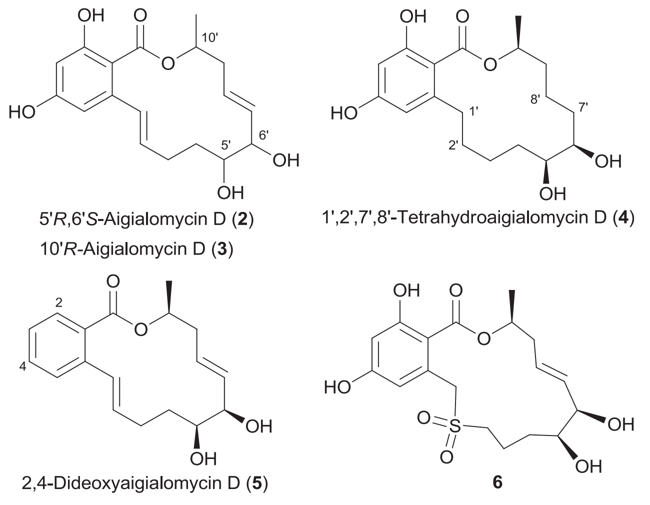
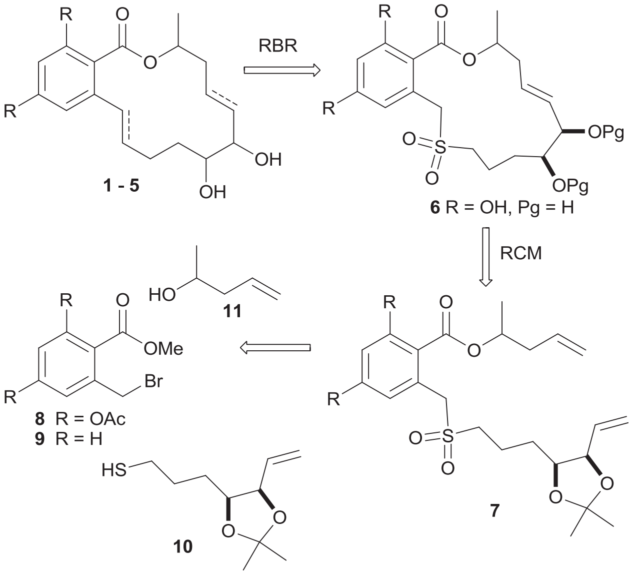


Fig. 2. Proposed analogues for this study.

During the course of the present study, Chen and co-workers reported syntheses of two of these AmD-based analogues (**3**, **4**), amongst others.[15] Their analogues were screened against CDK2 (a cyclin-dependent kinase) and MNK2 (a mitogen-activated protein kinase-interacting kinase that phosphorylates the oncogene eIF4E), which are both susceptible to AmD. 10′*R*-AmD (**3**) and 4-*O*-methyl-AmD were found to inhibit CDK2/cyclin A with similar potency to AmD, while 5′,6′-dideoxy-AmD, 5′,6′-acetonido-AmD and 7′,8′-dihydro-AmD were similarly active against MNK2.[26] TetrahydroAmD (**4**) did not show strong inhibition of either kinase.[15]

2. Results and discussion

The target analogues were prepared using a synthetic strategy related to that already reported by us for the total synthesis of AmD (Scheme 1).[20] The full carbon skeleton, **7**, would be accessed by substitution of the benzyl bromide **8** or **9** with thiol **10**, and esterification with the homoallylic alcohol **11**. Macrocycle formation would be achieved through ring-closing metathesis (RCM) of the benzylic sulfone **7**. A subsequent Ramberg–Bäcklund reaction (RBR) would provide the styrene moiety of analogues **1**–**5**, while the RBR step would be omitted for the sulfone analogue **6**.



Scheme 1. Retrosynthesis of proposed analogues **1**–**6**.

Benzylic bromide **8** was to be prepared from methyl orsellinate (**12**), as before.[20] The latter compound has been prepared numerous times by Claisen self-condensation of methyl acetoacetate and subsequent cyclisation of the resulting triketoester (Scheme 2).[27,28] Good yields are typically obtained by isolating the triketoester and allowing the subsequent cyclisation to occur under (usually) basic conditions.[27,29] A one-pot method, developed to expedite the synthesis, was reported to afford methyl orsellinate in a 60% yield.[28] However, in our hands, the one-pot variant gave consistently poor results (≤40% yield).[20] As part of our analogue studies, we had