Tetrahedron xxx (2018) 1–9

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of the C1 to C13 tetrahydropyranyl-resorcylate core of paecilomycin B

Rosa Cookson [1], Andrew J.P. White, Anthony G.M. Barrett*

Department of Chemistry, Imperial College, London, SW7 2AZ, England, UK

ARTICLE INFO

Article history:
Received 28 February 2018
Received in revised form
27 May 2018
Accepted 29 May 2018
Available online xxx

Keywords:
Biomimetic synthesis
Resorcylic acid lactone
Retro-Diels-Alder
Ketene
Macrocycle

ABSTRACT

A D-Glucose derived tetrahydropyran was converted into the C1 to C13 tetrahydropyranyl-resorcylate core of paecilomycin B in seven steps. Key transformations included the synthesis of a diketo-ester dioxinone, which upon thermolysis underwent a retro-hetero-Diels-Alder fragmentation to generate an acyl ketene. This was subsequently trapped by a secondary alcohol affording a triketo-ester, which was efficiently aromatized to produce the advanced resorcylate intermediate.

1. Introduction

Paecilomycin B (**2**) was isolated in 2010 by Wei and coworkers, along with a further five, novel resorcylic acid lactones (A-F; **1**–**6**) from a mycelial solid culture of *Paecilomyces* sp. SC0924 (Fig. 1).[1] This class of natural products contains the 6-alkyl-2,4-dihydroxybenzoic acid or β-resorcylate unit, which forms part of a macrolactone ring. These natural products were assessed for their antiplasmodial activity and paecilomycin B (**2**) was shown to have activity (IC_{50} 3.8 μM) against *Plasmodium falciparum* lines 3D7, a chloroquine-susceptible line. Further to this, results from a cytotoxicity assay showed paecilomycin B to be relatively non-cytotoxic ($IC_{50} > 50$ μM). There has been one reported total synthesis of paecilomycin B (**2**) (longest sequence 24 steps) by Ohba and Nakata in 2015.[2] In this paper, 2,4,6-tri*iso*propylphenyllithium mediated functionalization of a key aryl intermediate, based on the earlier work of Brimble,[3] and Fürstner[4] macrocyclization by ring closing metathesis (RCM) were used as key transformations.

The Barrett group has previously developed a biomimetic synthesis of such resorcylate natural products.[5] This work, which was inspired by the seminal work of Hyatt,[6] Harris[7] and Boeckman,[8] utilizes the dioxinone moiety to generate triketo-ketene intermediates. These were trapped by reaction with an appropriate alcohol; sequential aromatization of the resultant β,δ,ζ-triketo-esters of lactones gave the corresponding resorcylates (**10**) (Scheme 1). This methodology has been applied in the total synthesis of natural products including the estrogen agonist (*S*)-(−)-zearalenone, the antimalarial aigialomycin D and antibiotics 15G256 π, ι, and β.[9–11] However, in order to expand the methodology further, the group was interested in the synthesis of paecilomycin B (**2**) as a result of the presence of its unique transannular tetrahydropyran functionality.

2. Results and discussion

Wei reported that upon treatment of paecilomycin A (**1**) with 20% H_2SO_4, paecilomycin B (**2**) was formed as the major product.[1] We therefore sought to exploit this reasonable possible biomimetic transformation, thereby accessing both natural products. The retrosynthetic analysis of paecilomycin B (**2**), where it was proposed that a ring closing metathesis could be used for macrocyclization, is shown in Scheme 2. Resorcylate **11** would in turn be prepared from dioxinone **15** *via* diketo-dioxinone **13**.

Commercially available D-erythrolactone **16** was converted into the Weinreb amide, which was protected and reduced with DIBAl-H to give aldehyde **17** in 69% yield over three steps (Scheme 3). Subsequent Brown allylboration with a hydrogen peroxide work up

* Corresponding author.
E-mail addresses: agmb@ic.ac.uk, agm.barrett@imperial.ac.uk (A.G.M. Barrett).
[1] Current address: GlaxoSmithKline R&D, Stevenage, Hertfordshire, SG1 2NY, England.

https://doi.org/10.1016/j.tet.2018.05.083
0040-4020/

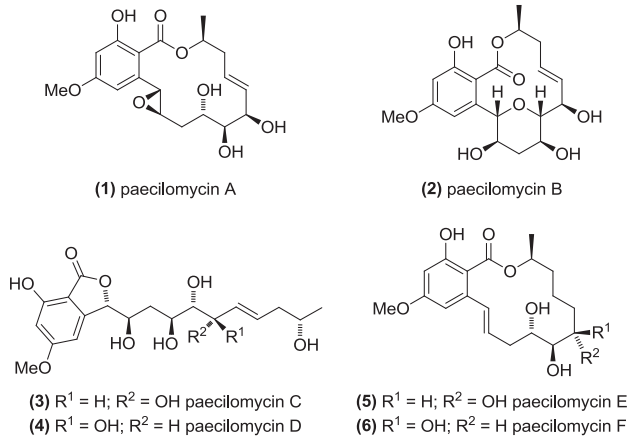
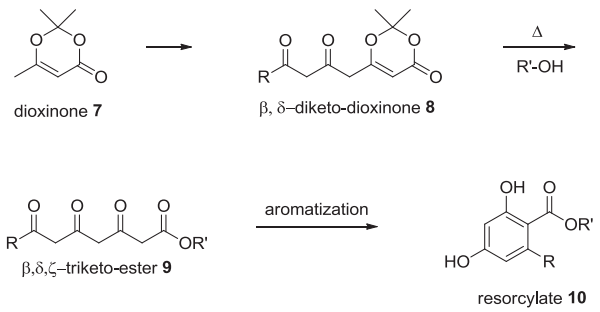


Fig. 1. Paecilomycins A-F.



Scheme 1. Barrett group synthesis of resorcylates.

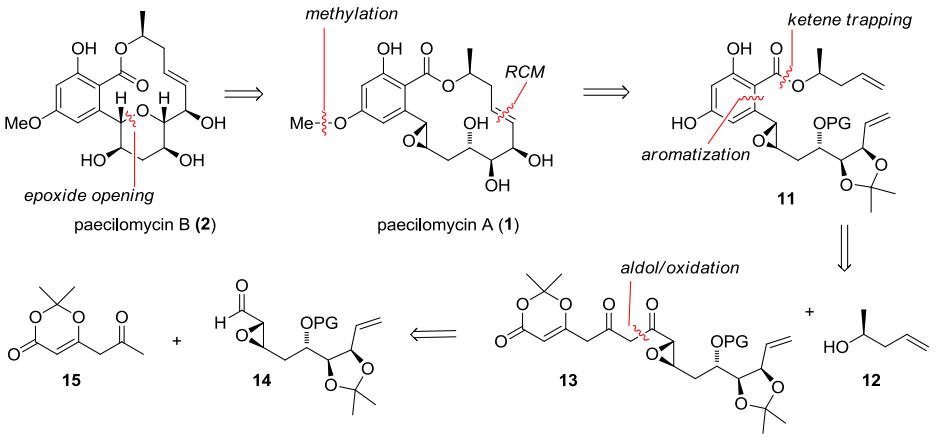
and silyl protection gave alkene **18**, which was subject to a cross metathesis with methyl acrylate thereby generating enoate **19**. Further DIBAl-H reduction gave the allylic alcohol, which was subject to diastereoselective epoxidation using *t*-butyl hydroperoxide catalyzed by $VO(acac)_2$ to provide epoxy-alcohol **20** (46%, two steps) as a single diastereoisomer. The alternative Sharpless epoxidation reaction was found to be low yielding, however gave the same epoxide as the major diastereoisomer thereby tentatively establishing its stereochemistry. This was confirmed by X-ray crystal structure determination (see Supporting Information). Subsequent Dess Martin periodinane oxidation of alcohol **20** gave aldehyde **21**.

Unfortunately, it was found at this stage that addition of the keto-dioxinone functionality by aldol[12] or *C*-acylation[13,14] reactions of the dianion derived from dioxinone **15**[9] with the aldehyde **21**, acyl imidazole **24** or Weinreb amide **25**, all proved to be untenable (Scheme 4) and gave only intractable mixtures of products. Furthermore, when these conditions were applied to a model aldehyde **26**,[12] no useful product was obtained thereby confirming that all our dioxinone homologation reactions[5] were incompatible with the α,β-epoxy-aldehyde functionality. As a result, an alternative route was examined.

Considering these problems, a second retrosynthetic analysis of paecilomycin B (**2**) was proposed. This incorporated the tetrahydropyranyl ring prior to generation of the diketo-dioxinone moiety (Scheme 5). As with the previous approach, a ring closing metathesis was envisaged as the key macrocyclization process. Given the fact that the functionality and stereochemistry of the tetrahydropyranyl ring substituents in intermediate **27** closely resembled those of D-glucose, we sought to use this sugar as an inexpensive starting material.

C-3 Deoxygenation of 1,6-anhydro-β, D-glucose **28** was carried out by selective double *p*-chlorobenzylation (68%), a process known for related benzylation reactions.[15] Subsequent Barton McCombie[16] deoxygenation of the imidazolylthiocarbonyl derivative of alcohol **29** provided the deoxy-glucose derivative **30** (84%) (Scheme 6). Subsequent boron trifluoride catalyzed reaction with acetic anhydride gave diacetate **31** (97%) with an anomeric selectivity of 3.3:1 (α: β). For a mechanistically similar reaction see the work of Zhao.[17] This ester was converted to nitriles **32** and **33** by reaction with trimethylsilyl cyanide catalyzed by trimethylsilyl triflate, and these products were separated by chromatography. Unfortunately, all attempts to convert the undesired nitrile **32** into its anomer **33** under either basic reaction conditions or resubmitting to further reaction with trimethylsilyl cyanide and trimethylsilyl triflate failed. Methanolysis of nitrile **33** in the presence of potassium carbonate gave the primary alcohol **34** (86%), which was protected as its *p*-bromo-benzyl ether **35** (93%). Our use of both the *p*-chlorobenzyl and *p*-bromobenzyl protecting groups was based on the expected preferential deprotection of the later by palladium catalyzed amination, a method introduced by Buchwald and Seeberger.[18] Finally, nitrile **35** was converted into the carboxylic acid **36** (97%) required for subsequent *C*-acylation reactions.

Attempts to condense the aldehyde, acyl chloride, imidazolide or Weinreb amide derived from carboxylic acid **36** with the dianion generated from keto-dioxinone **15**[5] failed to produce characterizable products. However, the methodology introduced during our total syntheses of 15G256 π, ι, and β[11] was successful in this key



Scheme 2. Retrosynthetic analysis of paecilomycin B (**2**).

Please cite this article in press as: Cookson R, et al., Synthesis of the C1 to C13 tetrahydropyranyl-resorcylate core of paecilomycin B, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.05.083