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Total synthesis and cytotoxic activity of dechlorogreensporones A and D

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ABSTRACT

The first and convergent total syntheses of polyketide natural products dechlorogreensporones A and D have been accomplished in 17 longest linear steps with 2.8% and 5.4% overall yields, respectively, starting from known methyl 2-(2-formyl-3,5-dihydroxyphenyl)acetate and commercially available *R*-(+)-propylene oxide and 1,2-epoxy-5-hexene. Our synthesis exploited key Mitsunobu esterification and (*E*)-selective ring-closing metathesis (RCM) to assemble the macrocycles as well as a Jacobsen hydrolytic kinetic resolution to install the stereogenic centers. Both synthetic compounds were found to display significant cytotoxic activity against seven human cancer cell lines with the IC_{50} ranges of 6.66–17.25 μM.

1. Introduction

The well-known 14-membered β-resorcylic acid lactones (RALs) are a group of fungal polyketide metabolites that possess a multitude of biological and pharmacological activities [1]. A subclass of RALs are those containing an α,β-unsaturated ketone at the 8–10 positions, which are derivatives of radicicol [2]. The major examples of this subclass of RALs are the pochonins [3] and the monocillins [4] (Fig. 1). This group of metabolites has been shown to exhibit various interesting biological activities e.g. antiviral activity against Herpes Simplex Virus 1 (HSV 1) [3a], antifungal activity (against *Mucorflavas* IFO 9560) [5], HSP-90 inhibitory activity [6], and latent HIV-1 reactivation activity [3c]. In consequence of their diverse and promising biological properties and structural features, this class of macrolides has been synthetic targets for many synthetic organic research groups worldwide [7]. Precedented strategies to construct the macrocyclic cores of RALs possessing similar core skeleton mainly relied on esterification reaction [7] and ring-closing metathesis [7c,f-k] (Fig. 2). Other key bond formations included Pd-catalyzed cross coupling/elimination [7a,b,d,e], substitution by dithiane anion [7c] and nucleophilic addition to Weinreb amide (acylation) [7f-i].

Dechlorogreensporones A (**5**) and D (**6**) are new 14-membered β-RALs, which were isolated, along with other 12 new RALs from a culture of a freshwater fungus *Halenospora* sp. by Oberlies and co-workers in 2014 (Fig. 3) [8]. Compounds **5** and **6** are radicicol analogues possessing a methoxy group at the 16-position, which represent rare examples of RALs containing β-resorcylic acid monomethyl ethers. Dechlorogreensporones A and D have the same planar structure which includes a stereogenic center at the 2-position. However, the minor structural difference is that **5** contains a keto group at the 5-position, whereas **6** bears an alcohol stereogenic center. In addition, dechlorogreensporone A (**5**) is structurally very similar to the previously reported natural product cryptosporiopsin A [9]. The absolute configuration of the C-2 asymmetric carbon in macrolactones **5** and **6** and other co-metabolites was proposed by the isolation group to be *S* by the evidence of X-ray diffraction analysis of the bromobenzoyl derivative of one of the metabolites in the series. The absolute configuration of the C-5 in **6** and co-metabolites containing C-5 alcohol stereogenic center was assigned to be *S* via a Mosher's ester method. Interestingly, the assigned C-2 absolute configuration of **5** and **6** and other analogues

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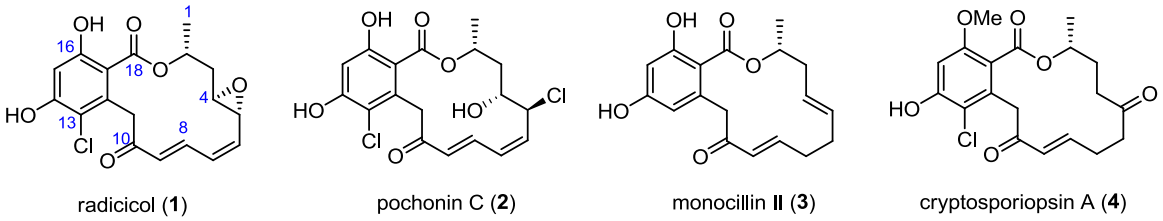

Fig. 1. Structures of radicicol and selected examples of its analogues.

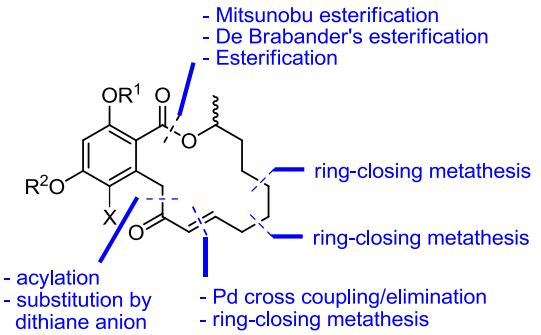

Fig. 2. Key bond formation strategies in previous syntheses of radicicol and its analogues.

in the series is opposite to that of cryptosporiopsin A, which was assigned by analogy to the known RAL pochonin D. Dechlorogreensporones A and D were tested for cytotoxic activities against two human cancer cell lines and were found to exhibit cytotoxicity against the MDA-MB-435 (melanoma) cancer cell line with IC_{50} values of 14.1 and 11.2 μM, respectively. They also exhibited cytotoxicity against the HT-29 (colon) cancer cell line with IC_{50} values of >20 and 25.4 μM, respectively. Due to promising biological activities of this subclass of RALs and our ongoing program for anticancer drug discovery, our research group has been focusing on a synthetic program of selected compounds of this class. Herein, we report the first total synthesis of both **5** and **6** as well as evaluation of their cytotoxic activity against seven human cancer cell lines.

2. Results and discussion

Our retrosynthetic approach toward dechlorogreensporones A (**5**) and D (**6**) would utilize similar disconnection strategy to Mohapatra and Thirupathi's [7j] and our previous report [7k] via ring-closing metathesis (RCM) as a key macrocyclization protocol and to concomitantly establish the (*E*) geometry of C8–C9 olefin. We would also rely on the Mitsunobu esterification to construct the ester functional group of the diene RCM precursor (Scheme 1). Although the targets **5** and **6** only differ by the functional groups at the 5-position and could be ideally synthesized from the same

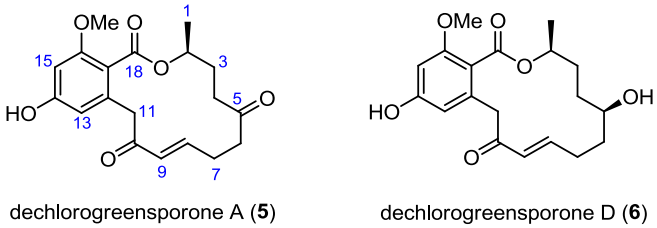

Fig. 3. Structures of dechlorogreensporones A (**5**) and D (**6**).

intermediate, the alcohol stereogenic center at the 5-position in **6** posed a challenge to the synthesis. Thus, we employed two different routes for the synthesis of the requisite alcohol fragments in conjunction with protecting group manipulation. The diene RCM precursor **9** (for **5**) or **10** (for **6**) would be assembled by Mitsunobu esterification between the common benzoic acid intermediate **11** and chiral alcohol intermediate **12** or **13**. The common benzoic acid intermediate **11** would be elaborated from the known phenol **14** using our previously described approach. The requisite chiral alcohol **12** for the synthesis of **5** would be obtained from *R*-(+)-propylene oxide (**15**) via double allylation, whereas enantioenriched alcohol **13** would be prepared from 1,2-epoxy-5-hexene (**16**) using Jacobsen hydrolytic kinetic resolution to construct both chiral centers [10].

Synthesis of benzoic acid **11** which was required as a Mitsunobu coupling partner for syntheses of both **5** and **6** commenced with selective protection of known phenol **14** [11] with 4-methoxybenzyl ether (PMB) group [12] to afford PMB ether **17** in 82% yield. Subsequent methylation of the remaining phenol moiety with iodomethane and K_2CO_3 in DMF furnished methyl ether **18** in 94% yield. Following our previously established sequence [7k], benzaldehyde **18** was further elaborated to the requisite benzoic acid **11** in 10 steps and 31% overall yield (Scheme 2).

Synthesis of alcohol **12** required for the synthesis of **5** was achieved in a concise sequence of 6 steps as illustrated in Scheme 3. Regioselective ring opening of commercially available *R*-(+)-propylene oxide (**16**) (>99% ee) by allylmagnesium bromide in the presence of catalytic CuI provided the corresponding chiral secondary alcohol [13], which was instantaneously protected with TBDPS group to afford TBDPS ether **19** in 78% yield over 2 steps. Subsequent epoxidation of alkene **19** with *m*-CPBA afforded racemic epoxide **20**, which was then subjected to another regioselective ring opening by allylmagnesium bromide to give racemic alcohol **21** in 89% yield [14]. Protection of the secondary alcohol of **21** with ethoxymethyl (EOM) group provided EOM ether, which after TBDPS deprotection with TBAF furnished the desired chiral alcohol **12** in 95% yield. The absolute configuration of the alcohol stereogenic center was confirmed to be *R* based on Mosher ester analysis.

Having successfully synthesized both key fragments **11** and **12**, we continued to complete the synthesis of dechlorogreensporone A (Scheme 4). Benzoic acid **11** was subjected to esterification with (*R*)-alcohol **12** under Mitsunobu conditions using diisopropyl azodicarboxylate (DIAD) and PPh_3 in toluene at room temperature to smoothly furnish the ester RCM diene precursor **9** in 72% yield. This step was expected to provide the correct stereochemistry of the C-2 stereogenic center. With diene **9** in hand, the stage was then set for the key ring-closing metathesis. We and the Mohapatra group have previously demonstrated that the second-generation Grubbs catalyst is a remarkable RCM catalyst for this type of substrate [7j,k]. However, in this case the second-generation Grubbs catalyst proved to be less reactive and led to incomplete consumption of the starting diene. To our delight, RCM of **9** using 10 mol% of second-