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Total Synthesis of (+)-Grandifloracin by Iron Complexation of a Microbial Arene Oxidation Product

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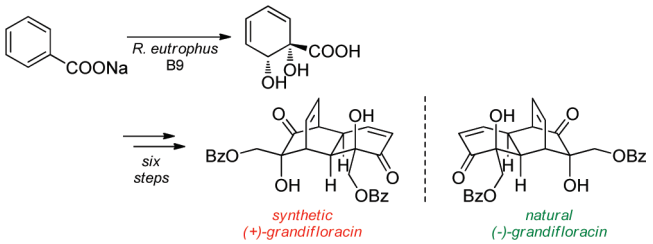
ABSTRACT



(+)-Grandifloracin was synthesized from sodium benzoate by means of a dearomatizing dihydroxylation that proceeds with unusual regioselectivity. Iron diene complexes formed from the arene oxidation product permit the use of otherwise inaccessible transformations. The synthetic material was shown to be antipodal to the natural product, thus determining the absolute configuration of grandifloracin for the first time.

(−)-Grandifloracin was first isolated in 1997 from *Uvaria grandiflora*[1] and has subsequently been isolated from *Uvaria rufa*[2a] and *Uvaria calamistrata*.[2b] A concise total synthesis of (±)-grandifloracin has been reported by Quideau and co-workers,[3] but no enantioselective syntheses have been reported to date. The absolute configuration of grandifloracin has not previously been established unambiguously. The structure **1** shown in Figure 1 depicts the absolute configuration expected upon comparison of the grandifloracin structure with the coisolated natural product uvarirufone A (**2**), for which the absolute configuration is reported.[2a] However, there has been disagreement in the literature on the absolute structure of a second coisolate, tonkinenin A.[2a] This was initially assigned the structure **3**,[4a] but subsequent total synthesis led to revised structure **4** being proposed[4b−f] (structure **3** is nevertheless still being propagated in the literature[2a]). Structure **4** is zeylenone, a third coisolate of grandifloracin,[1] implying that zeylenone and tonkinenin A are in fact the same compound. Furthermore, naturally occurring zeylenone derivatives such as 3-*O*-debenzoylzeylenone **5** reportedly

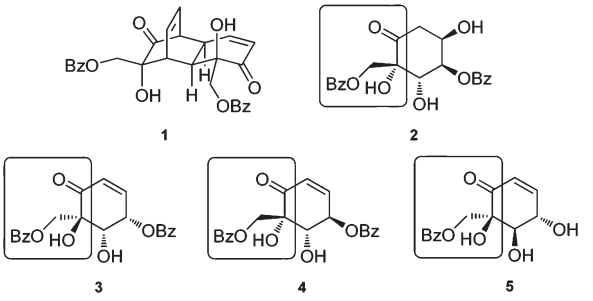


Figure 1. Grandifloracin **1** (one possible enantiomeric structure shown) and related natural products.

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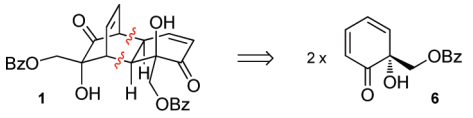
have the *opposite* absolute configuration to zeylenone **4**, as shown by chemical correlation.[5] This implies that *both* configurations at the quaternary center are biosynthetically accessible, a proposal supported by previous work on the biosynthesis of α- and *β*-senepoxide and related cyclohexene oxides.[6] In view of the above ambiguity, confirmation of the absolute configuration of grandifloracin by total synthesis is required.

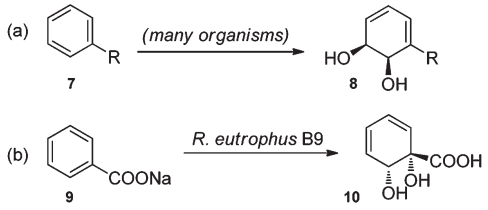
Grandifloracin is believed to arise by the cyclodimerization of 2 equivalents of precursor **6** (Scheme 1). Cyclodimerizations of cyclohexa-2,4-dienones are known to exhibit remarkable levels of regio-, site-, and stereoselectivity, and the origins of this selectivity have been studied.[7] They have also been proposed to occur in the biosynthesis of related natural products; of these, total syntheses of aquaticol,[8,9] asatone,[10] biscarvacrol,[3,9,11] bisorbicillinol,[12] heterotropatrione,[13] and isoheterotropatrione[13] have been reported that exploit such dimerizations. Advanced intermediates toward bacchopetiolone[14] and celastroidins[15] accessed by such dimerizations have also been described.

Scheme 1. Proposed Biosynthetic Origin of Grandifloracin



Of these reported total syntheses, most accessed the dimerization precursor by oxidative dearomatization of a phenol, either by chemical[3,8,9,10c,11,12a−d,14,15] or electrochemical[10a,b,13] methods. In Deng's synthesis of bisorbicillinol[12e] an alternative approach was adopted, employing a Claisen condensation to access the dimerization precursor. In the context of grandifloracin, we have adopted a conceptually distinct approach, namely microbial arene dihydroxylation; this has not been employed to date to access cyclohexa-2,4-dienone dimer natural products.

Scheme 2. Regio- and Stereoselectivity of Dioxygenases



Enzymatic dihydroxylation of arenes to produce enantiopure building blocks is established methodology.[16] The most common regiochemical outcome is installation of the diol *ortho,meta* to the arene substituent (**8**, Scheme 2a).[17] However, *R. eutrophus* B9[18] and certain other organisms[19] are able to metabolize benzoate to the corresponding *ipso, ortho* diol (**10**, Scheme 2b). Chiron **10** has found diverse synthetic applications,[20] and we have demonstrated its use in a concise synthesis of new azacarbasugars.[21] The absolute configuration of **10** has been proven.[20a,b] Great synthetic utility derives from the densely packed, differentiated functionality in arene dihydrodiols. For example, **8** (R = C_2H_3) has been employed in the synthesis of zeylena, isolated from *Uvaria zeylanica*.[22] However, the use of arene dihydrodiols is sometimes hampered by their facile dehydration/rearomatization at extremes of pH or at elevated

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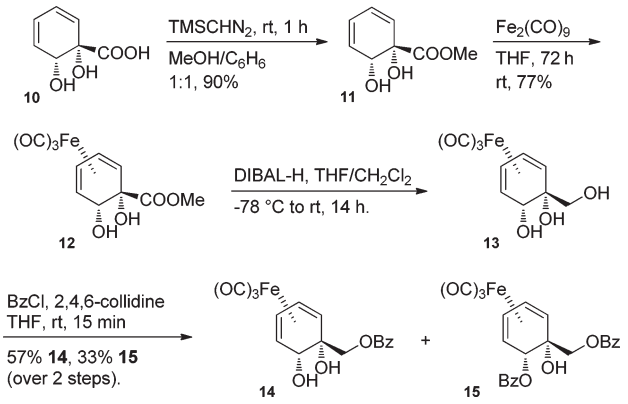
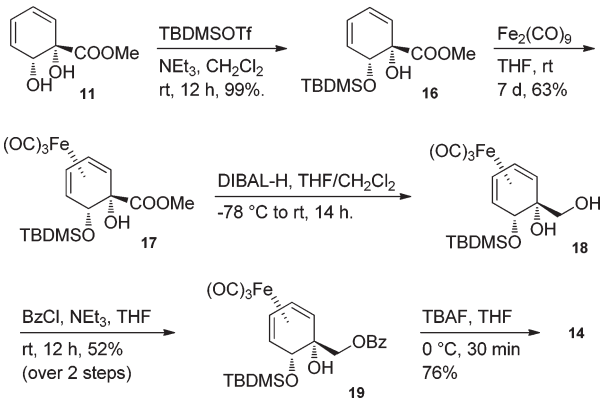
temperature. This decomposition pathway may be shut down by protection of the diene as a tricarbonyliron(0) complex. Many dienes of type **8** have been complexed in this fashion,[23] and we have recently extended this methodology to derivatives of **10**.[24] The iron complex serves not only as a protecting group but also allows access to new reactivity, e.g., formation of cationic η^5 dienyl complexes. In the present work, the combination of diol acid **10** with tricarbonyliron methodology permits rapid assembly of (+)-grandifloracin **1**.

Scheme 3. Route to Benzoylated Iron Complex



Diol acid **10** was treated with TMS-diazomethane to afford methyl ester **11**. Exposure of this to nonacarbonyl diiron gave complex **12** as the sole diastereoisomer, as proven previously by crystallography.[24a] Reduction of **12** with diisobutylaluminum hydride furnished triol **13**, which was used crude due to its instability. The success of this reduction illustrates the necessity of using the iron complex, as attempted reduction of the corresponding uncomplexed ester **11** results only in aromatization under all conditions we have tried. Selective access to benzoate **14** proved problematic, with appreciable benzoylation at the secondary alcohol also observed. It was established that premixing benzoyl chloride and 2,4,6-collidine prior to addition to **13** minimized formation of dibenzoate **15** (Scheme 3).[25]

Scheme 4. Alternate Route Employing Silicon Protection



In order to circumvent problems of overacylation, an alternative route was explored. Selective silylation of the secondary alcohol in **11** was followed by iron complex formation as before (Scheme 4). Notably, the sole diastereomer isolated (**17**) was again that in which iron complexed to the lower face, despite the increased steric blockade due to the silyl ether (the structure was confirmed by X-ray crystallography, Figure 2). Reduction was effected as previously with diisobutylaluminum hydride (the uncomplexed ester **16** once again not being amenable to direct reduction). Treatment of **18** with BzCl led to monobenzoylation only, as expected, and TBAF-mediated desilylation furnished **14**. However, the overall yield of **14** by this route (25% from **11**) is inferior to that in Scheme 3 (44% from **11**).[26]

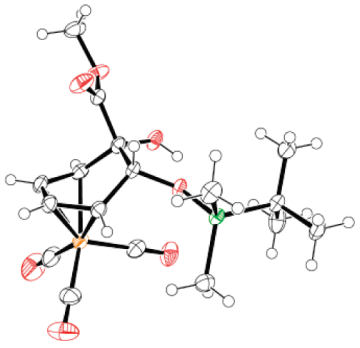


Figure 2. ORTEP diagram of **17** shows ellipsoids at 50% probability. H atoms are shown as spheres of arbitrary radius.

We[24a] and others[27] have shown that in certain cases MnO_2 may be used to effect chemoselective alcohol

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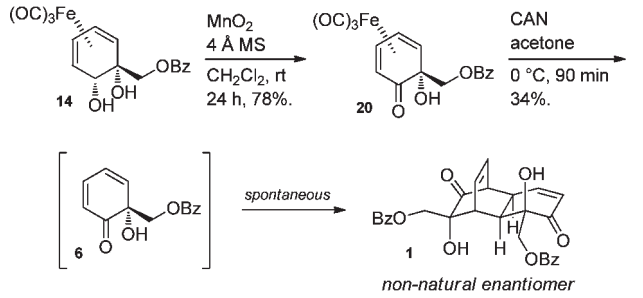
Scheme 5. Total Synthesis of (+)-Grandifloracin **1**



oxidation in tricarbonyliron diene complexes, leaving the oxidatively labile tricarbonyliron fragment intact. Upon exposure of **14** to MnO_2, complexed cyclohexadienone **20** was accessed in good yield; as expected, this proved inert with respect to dimerization. The utility of iron complexation is further underscored by the facile access to **20**; upon attempted oxidation with MnO_2, uncomplexed alcohols **10** and **11** give predominantly rearomatized material and only very low yields of cyclohexadienone dimers.[28] A second discrete oxidation of **20** was then required to liberate the uncomplexed dienone. Trimethylamine *N*-oxide, although commonly used for cleavage of tricarbonyliron,[29] was ineffective in the case of **20**. Instead, CAN in acetone was found to unmask the diene giving **6**, with spontaneous dimerization affording (+)-grandifloracin **1** (six steps from **10**, 10% overall yield, Scheme 5).

^1H and ^{13}C NMR data for synthetic **1** were in agreement with those reported for the natural product.[1,2] Two values have been reported for the optical rotation of natural grandifloracin, $[\alpha]_D$ −13.6 (*c* 0.728, $CHCl_3$)[1a] and $[\alpha]_D$ −0.02 (*c* 0.04, $CHCl_3$).[2b] The measured optical rotation for synthetic grandifloracin **1** is $[\alpha]_D$ +10.6 (*c* 0.90, $CHCl_3$). The magnitude of this value accords well with the first literature value; the opposite sign indicates that the (+)-**1** we have synthesized is in fact *ent*-grandifloracin.

In summary, we have reported a concise synthesis of (+)-*ent*-grandifloracin **1** that showcases the synthetic utility of arene dihydrodiols in conjunction with iron complexation methodology. The work serves to establish the absolute configuration of natural (−)-grandifloracin. Further work on the use of arene dihydrodiol **10** and its iron complexes in total synthesis is underway and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and ^1H NMR and ^{13}C NMR spectra for all novel compounds, as well as selected 2D-NMR data. Circular dichroism spectrum for synthetic (+)-**1**. Crystallographic data for **17** (CCDC 822156).This material is available free of charge via the Internet at http://pubs.acs.org.

(28) Both **11** and a derivative protected with a BOM group undergo oxidation to the corresponding cyclohexa-2,4-dienones upon treatment with Dess−Martin periodinane; see refs 20b and 20h.

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