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 grandiflora1 and has subsequently been isolated from Uvaria rugosa2a 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 proposed4b−f (structure 3 is nevertheless still being propagated in the literature2a). 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-debenzylozylenone 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, as shown by chemical correlation. 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. 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 cycldimerization of 2 equivalents of precursor 6 (Scheme 1). Cycldimerizations 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. They have also been proposed to occur in the biosynthesis of related natural products; of these, total syntheses of aquaticol, atone, bisascarvacrol, bisorbicillinol, heterotropatrine, and isoheterotropatrine have been reported that exploit such dimerizations. Advanced intermediates toward bacchopetiolone and cestroides accessed by such dimerizations have also been described.

Of these reported total syntheses, most accessed the dimerization precursor by oxidative dearomatization of a phenol, either by chemical or electrochemical methods. In Deng’s synthesis of bisorbicillinol 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 arenne dihydroxylation; this has not been employed to date to access cyclohexa-2,4-diene dimer natural products.

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**Scheme 1. Proposed Biosynthetic Origin of Grandifloracin**

![Biosynthetic Origin Diagram]

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**Scheme 2. Regio- and Stereoselectivity of Dioxygenases**

![Dioxygenases Diagram]

Enzymatic dihydroxylation of arenes to produce enantiopure building blocks is established methodology. The most common regiochemical outcome is installation of the diol ortho,meta to the arenne substituent. However, R. eutrophus B918 and certain other organisms are able to metabolize benzoate to the corresponding ipso, ortho diol. Chiron 10 has found diverse synthetic applications, and we have demonstrated its use in a concise synthesis of new azacarbasugars. The absolute configuration of 10 has been proven. Great synthetic utility derives from the densely packed, differentiated functionality in arenne dihydrodiols. For example, (R = C6H5) has been employed in the synthesis of zeylenol isolated from *Uvaria zeylanica*. However, the use of arenne dihydrodiols is sometimes hampered by their facile dehydration/rearomatization at extremes of pH or at elevated temperatures.

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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 η5-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 disobutylaluminum 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 benzylation at the secondary alcohol also observed. It was established that premixing benzoyl chloride and 2,4,6-collidine prior to premixing benzoyl chloride and 2,4,6-collidine prior to

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 disobutylaluminum hydride (the uncomplexed ester 16 once again not being amenable to direct reduction). Treatment of 18 with BzCl led to monobenzylation 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 MnO2 may be used to effect chemoselective alcohol

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oxidation in tricarbonyliron diene complexes, leaving the oxidatively labile tricarbonyliron fragment intact. Upon exposure of 14 to MnO2, 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 MnO2, 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 13C 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, [α]D –13.6 (c 0.728, CHCl3)1a and [α]D –0.02 (c 0.04, CHCl3).2b The measured optical rotation for synthetic grandifloracin 1 is [α]D +10.6 (c 0.90, CHCl3). 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 13C 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.