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 since been isolated from Uvaria rufa2a 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-debenzoylzeylenone 5 reportedly...
have the opposite absolute configuration to zeylenone 4, 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 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. They have also been proposed to occur in the biosynthesis of related natural products; of these, total syntheses of aquaticol, asatone, biscarvacrol, heterotropatrine, and isoheterotropatrine have been reported that exploit such dimerizations. Advanced intermediates toward bacchopetiolone14 and celastroidins15 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 dimerization precursor by oxidative dearomatization of a phenol, either by chemical methods. In Deng’s synthesis of bisorbicillinol 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, asatone, biscarvacrol, heterotropatrine, and isoheterotropatrine have been reported that exploit such dimerizations. Advanced intermediates toward bacchopetiolone and celastroidins accessed by such dimerizations have also been described.

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

Scheme 3. Route to Benzoylated Iron Complex

Diol acid \( \mathbf{10} \) was treated with TMS-diazomethane to afford methyl ester \( \mathbf{11} \). Exposure of this to nonacarbonyl diiron gave complex \( \mathbf{12} \) as the sole diastereoisomer, as proven previously by crystallography. Reduction of \( \mathbf{12} \) with diisobutylaluminum hydride furnished triol \( \mathbf{13} \), 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 \( \mathbf{11} \) results only in aromatization under all conditions we have tried. Selective access to benzoate \( \mathbf{14} \) 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 secondary alcohol also observed. It was established that premixing benzoyl chloride and 2,4,6-collidine prior to

In order to circumvent problems of overacylation, an alternative route was explored. Selective silylation of the secondary alcohol in \( \mathbf{11} \) was followed by iron complex formation as before (Scheme 4). Notably, the sole diastereomer isolated (\( \mathbf{17} \)) 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 as expected, and TBAF-mediated desilylation furnished \( \mathbf{14} \). However, the overall yield of \( \mathbf{14} \) by this route (25% from \( \mathbf{11} \)) is inferior to that in Scheme 3 (44% from \( \mathbf{11} \)).

Figure 2. ORTEP diagram of \( \mathbf{17} \) shows ellipsoids at 50% probability. H atoms are shown as spheres of arbitrary radius.

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Scheme 4. Alternate Route Employing Silicon Protection

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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.