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Total Synthesis and Absolute Stereochemical Assignment of the Insecticidal Metabolites Yaequinolones J1 and J2

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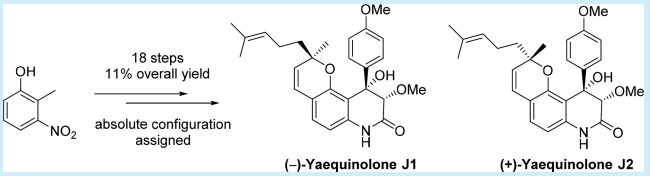
Supporting Information

ABSTRACT: A highly stereocontrolled total synthesis of (−)-yaequinolone J1 and (+)-yaequinolone J2 was accomplished using an Evans auxiliary to establish a *syn*-diol unit in an acyclic appendage to a preformed benzopyran core bearing a homoprenyl group. The first total synthesis of a complex member of this family of 3,4-dioxygenated 3,4-dihydro 4-aryl quinolin-2-(1*H*)-ones also allowed the assignment of absolute stereochemistry, thereby suggesting the same for several members of this family of biogenetically related alkaloids hitherto reported with relative configurations of stereogenic carbons for some and absolute assignments relying on empirical data for others.



Alkaloids comprising the quinolone core isolated primarily from terrestrial plants are among the most abundant biologically relevant natural products.[1] Among this important family is a new group of oxygenated congeners that have recently emerged with diverse biological activities particularly as insecticides[2,3] as well as antiviral[4] and anticancer agents.[5] The first report of such metabolites isolated from *Penicillium sp.* NTC-47 revealed the existence of 3,4-dioxygenated 3,4-dihydro 4-aryl quinolinones, for which only relative stereochemistries were assigned.[2] In the ensuing 20 years since the initial report, a plethora of 3,4-dioxygenated 3,4-dihydro 4-aryl quinolin-2-(1*H*)-ones and their 5-hydroxy variants (Figure 1) have been isolated from plant and marine fungi and their biological activities evaluated.[6] Interest in this family of natural products has grown exponentially over the past 20 years as manifested in the patent literature.[7] The stereochemistry of the majority of these fascinating metabolites has been studied by detailed NMR spectroscopic methods.[6,8] In some cases ECD (electronic circular dichroism) in conjunction with theoretical calculations have been used to propose absolute stereochemistry.[4,9,11] However, even when X-ray crystal structures were available, only relative stereochemistries could be assigned.[10,11]

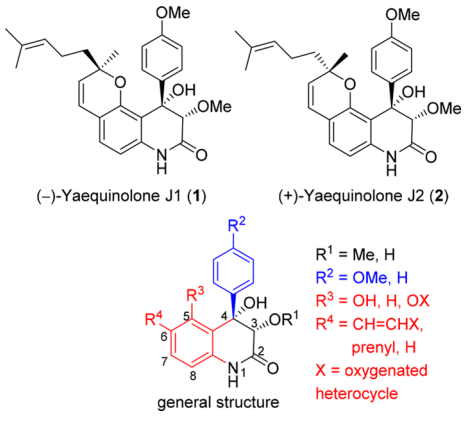


Figure 1. Revised absolute configuration of (−)-yaequinolone J1 (**1**) and (+)-yaequinolone J2 (**2**) and general structure of 3,4-dioxygenated 3,4-dihydro 4-aryl quinolin-2(1*H*)-ones (yaequinolone A2, R^1 = H, R^2 = OMe, R^3 = R^4 = H).

Elegant biosynthetic studies have revealed that the 4-methoxyphenyl (or phenyl) dihydroquinolone core originates from anthranilic acid and *O*-methyl tyrosine (or tyrosine) which involve discrete intermediates that are hydroxylated and eventually prenylated at a later stage to give a variety of prenyl and prenyl derived oxygenated heterocycles at C-6[12] (Figure 1).

In spite of their biological activities,[6] efforts toward the total synthesis of this class of 3,4-dioxygenated 3,4-dihydroquinolones in general have been sparse.[13] So far, among these fascinating compounds, only a total synthesis of racemic yaequinolone A2,[3] the structurally simplest member of this family, has been reported in 2009 by Pan and co-workers[14] (Figure 1).

In 2005, Tomoda and co-workers reported the isolation of two novel metabolites named yaequinolones J1 (**1**) and J2 (**2**) from a culture strain of *Penicillium sp.* FKI-2140, isolated from a soil sample collected at Ishigakijima Island, Okinawa Prefecture, Japan[15] (Figure 1). These metabolites showed growth inhibitory activity against *Artemia salina* (brine shrimp) with the same MIC value of 6.25 μg/mL. Extensive NMR studies including ^{1}H−^{1}H COSY and HMBC correlations, as well as NOE measurements, designated the relative stereochemistry of **1** as 3*R**4*R**3″*S**. Similar analysis of **2** led to an

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Org. Lett. XXXX, XXX, XXX–XXX

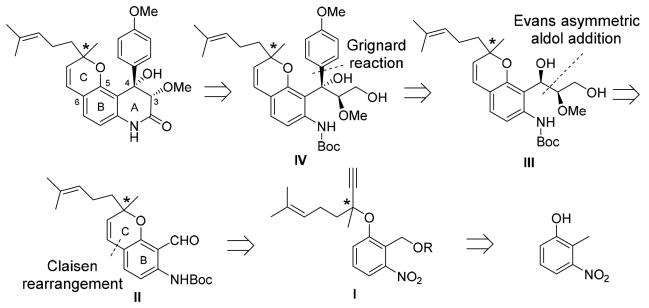
identical relative stereochemistry except for 3″ which was determined to be 3″*R**. Thus, the two metabolites differed only in the relative stereochemistry of the pyranyl tertiary carbon bearing the methyl group.

Herein we report the first asymmetric total synthesis of yaequinolones J1 (**1**) and J2 (**2**) as well as the establishment of their absolute stereochemistries. In considering various bond disconnections toward suitable building blocks, we were cognizant that the presence of a tertiary benzylic hydroxyl group could easily form stabilized cations leading to *β*-elimination and the formation of byproducts depending on the choice of reagents and reaction used. Moreover, we appreciated the challenge involved in securing the *syn*-stereochemistry of the C-3/C-4 diol unit with the required absolute configurations.

Based on the assumption that the relative stereochemistries as indicated by Tomoda and co-workers[15] corresponded to the proposed structures and in the absence of other confirming data, we completed the total synthesis of 3*R*, 4*R*, 3″*S* (+)-yaequinolone J1, only to realize that we had produced the enantiomer (*ent*-**1**) as indicated from the positive optical rotation value (see Supporting Information (SI)). With this knowledge, which is in full agreement with the proposals suggested for similar natural products of this family relying on ECD spectra,[4,9,11] we resumed our work toward the total synthesis of the stereochemically revised 3*S*, 4*S*, 3″*R* isomer.

For strategic considerations we chose to first address the synthesis of the homoprenylated pyran ring comprised within the B/C ring system of the target yaequinolones (Scheme 1).

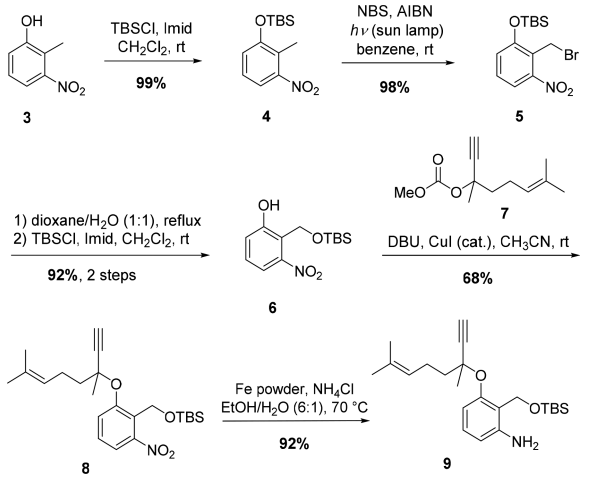
Scheme 1. Retrosynthetic Disconnection of Yaequinolones J1 (1) and J2 (2)[a]



[a]Asterisk denotes epimeric carbon.

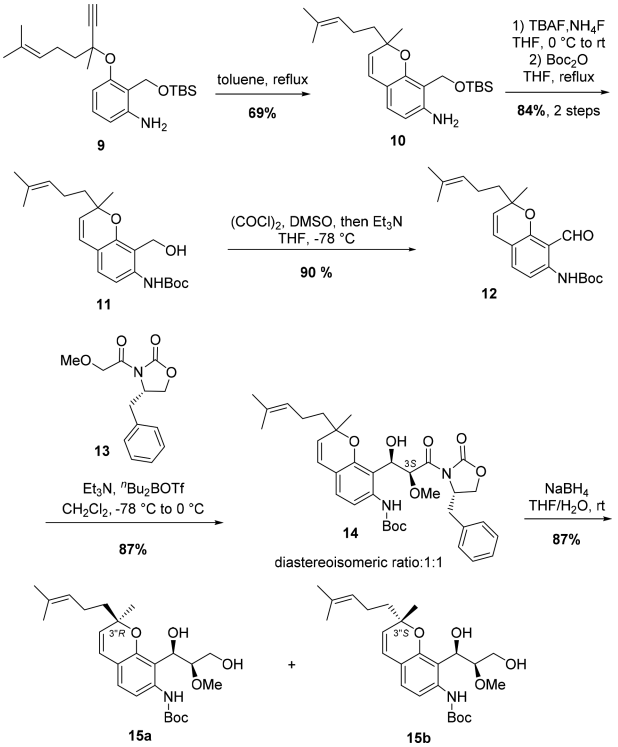
Retrosynthetically this could be accomplished through an *ortho*-Claisen rearrangement from **I** to **II**. Critical to the success of this strategy was to develop stereocontrolled reactions that would include two vicinal stereogenic carbon atoms bearing an *O*-methyl group and a tertiary benzylic alcohol as in **IV**. We considered that the Evans chiral auxiliary-mediated aldol reaction[16] to be admirably suited for the elaboration of C-2 bearing the *O*-methyl group with the desired 3*S* stereochemistry of the two natural products. Starting with 6-hydroxy-2-nitrotoluene **3**, protection as the OTBS ether **4**, bromination to **5**, and conversion to the silyloxymethyl intermediate **6**[17] proceeded in near-quantitative yield. A CuI catalyzed alkylation with the homoprenyl reagent **7**[18] afforded the ether **8**. Reduction of the nitro group in the presence of Fe powder[19] afforded the aniline **9** in high yield (Scheme 2).

Scheme 2. Synthesis of Aniline Derivative 9



Facile *ortho*-Claisen rearrangement[20] occurred in refluxing toluene to afford **10** which was converted to the *N*-Boc protected alcohol **11**. Swern oxidation led the aldehyde **12** which was subjected to an aldol reaction according to Evans[16] with the oxazolidinone **13**[21] derived from (*S*)-phenylalanine to afford a 1:1 inseparable mixture of diastereoisomers **14** differing in the configuration of the pyranyl tertiary methyl group (Scheme 3).

Scheme 3. Synthesis of Diols 15a and 15b



Remarkably, only one *syn*-aldol diol was produced with the desired 3*S*-configuration at the C-3 methoxy-bearing carbon. Reductive cleavage of the oxazolidinone[22] afforded the two diastereoisomers **15a** and **15b** in equal amounts which were separated by column chromatography (Scheme 3).

Isomer **15a** was converted to the ketone **16** in high overall yield. An X-ray crystal structure provided definitive proof of

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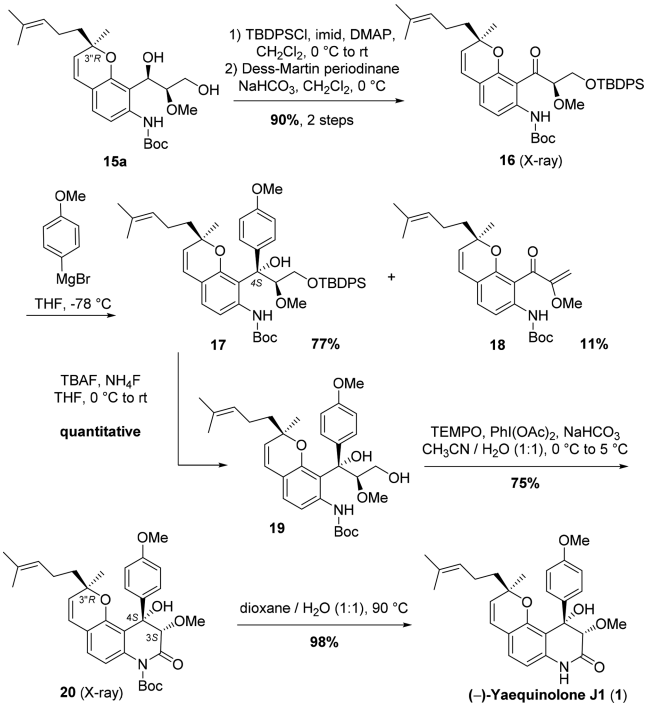
Org. Lett. XXXX, XXX, XXX−XXX

absolute 3″*R* stereochemistry (Scheme 4). Treatment of the ketone **16** with *p*-methoxyphenyl magnesium bromide was

Scheme 4. Synthesis of Yaequinolone J1 (1) from 15a



remarkably stereoselctive affording the desired 4*S* tertiary alcohol **17** in 77% yield along with 11% of elimination product **18**. It was imperative to conduct this reaction at −78 °C to minimize the *β*-elimination of the OTBDPS group. There remained cleaving the primary alcohol to afford **19** and finding a suitable oxidation method that would give an intermediate *N*-protected hemiaminal which could be further oxidized to the desired *N*-Boc dihydroquinolin-2-one **20**. Among the many oxidants that we tried (PDC, Corey−Schmidt, PCC), none were as effective and selective as the TEMPO, $PhI(OAc)_2$ combination.[23] This oxidizing system initially gave a hemiaminal intermediate which could be detected by NMR analysis after 3 h before further oxidation to the lactam took place. An X-ray crystal structure provided definitive proof of the global structure and, importantly, the expected *S*-stereochemistry at the benzylic carbon atom. To the best of our knowledge this TEMPO, $PhI(OAc)_2$ reagent combination has not been used for the direct synthesis of an *N*-Boc lactam from a primary alcohol. Being weary of the lability of the tertiary benzylic hydroxyl group under acidic conditions, and the ever-present problem of *β*-elimination, we were pleased that heating a dioxane−water solution[24] of **20** led to **1** as a white amorphous solid in nearly quantitative yield; $[\alpha]^{25}_{D} = -68.1°$ (c = 1.3, EtOH); reported[15] $[\alpha]^{23}_{D} = -65.6°$ (c = 0.1, EtOH).

Starting with the C-3″ epimeric intermediate **15b**, we also completed the total synthesis of (+)-yaequinolone J2, obtained as a white amorphous solid (see SI); $[\alpha]^{25}_{D} = +187.1°$ (c = 1.1, EtOH), reported[15] $[\alpha]^{23}_{D} = +181.7°$ (c = 0.1, EtOH).

To the best of our knowledge, the cytotoxicity of yaequinolones J1 and J2 against proliferating cancer cells have not been reported. Compared to data for other congeners,[5] our preliminary results in an *in vitro* assay showed highly promising EC_{50} values of 8.24 and 3.73 μM against a melanoma A375 cell line respectively as well as 3.38 and 4.08 μM against the colorectal HCT116 cell line.

In conclusion, we report the first asymmetric total synthesis of yaequinolones J1 (**1**) and J2 (**2**) accomplished in 18 steps with a global yield of 11% for both the natural products. With the establishment of their absolute stereochemical assignment through a total synthesis, other members of this biosynthetically related family of metabolites whose stereochemistries were previously assigned on a relative basis can now be configurationally correlated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01701.

Synthetic schemes for **1** and **2**, detailed experimental procedures in which IUPAC nomenclature and numbering was adopted, spectral data and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1826666−1826667 and 1826761 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.
The numbering used in the manuscript was the same as that in the original publication (ref 15) for consistency and in related papers and reviews (ref 6).

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■ DEDICATION

Dedicated to Professor David A. Evans for his scholarly and timely contributions to advance the science of asymmetric synthesis and catalysis.

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