Modular Terpenoid Construction via Catalytic Enantioselective Formation of All-Carbon Quaternary Centers: Total Synthesis of Oridamycin A, Triptoquinones B and C, and Isoiresin

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S *Supporting Information*

ABSTRACT: Total syntheses of oridamycin A, triptoquinones B and C, and isoiresin are accomplished from a common intermediate prepared via iridium-catalyzed alcohol C−H *tert*-(hydroxy)prenylation - a byproduct-free process that forms an all-carbon quaternary stereocenter with excellent control of diastereo- and enantio-selectivity.

Terpenoid natural products are a large class of secondary metabolites that have found broad use in human medicine, agriculture and the flavor/fragrance industry.[1] The biosynthesis[2] and *de novo* chemical synthesis[3] of terpenoid natural products is largely reliant on the cascade polycyclization of polyolefins.[2,3] While polycyclization strategies enable rapid increases in molecular complexity, their use in *de novo* chemical synthesis is often accompanied by a lack of convergency, impeding the design of more concise routes.[3c] Recently, in connection with the development of methods for direct alcohol C−H functionalization via C−C bond-forming transfer hydrogenation,[4] we devised a diastereo- and enantioselective protocol for primary alcohol C−H *tert*-(hydroxy)prenylation.[5] This process creates a structural motif bearing an all-carbon quaternary stereocenter that is found in over 2000 terpenoid natural products (eq 1).[1]


(eq. 1)

73 - 91% Yield
30 - >99:1 dr
91 - 99% ee%

A motif found in >2000 terpenoid natural products
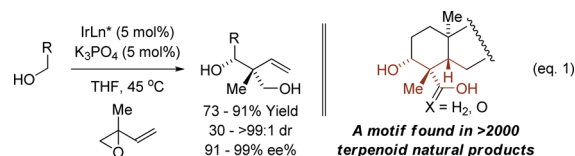
Here, our first efforts to utilize alcohol C−H *tert*-(hydroxy)-prenylation *vis-à-vis* terpenoid construction are described. This effort has resulted in the total synthesis of oridamycin A,[6,7] triptoquinones B and C,[8,9] and isoiresin[10,11] from a common intermediate (Figure 1). Notably, each natural product is prepared in fewer steps than in any prior approach[7,9,11] and, with the exception of isoiresin, protecting groups are not required. Thus, alcohol C−H *tert*-(hydroxy)prenylation offers a powerful, modular means of preparing diverse terpenoid natural products beyond cascade polycyclization.

Retrosynthetically, a modular strategy was envisioned (Scheme 1). The union of Fragment **A** with Fragment **B-I** or **B-II** via Suzuki cross-coupling followed by Friedel−Crafts cyclization serves as a conduit to oridamycin A and tripto-

Oridamycin A, R[1] = CO$_2$H, R[2] = Me
Li 2015, 10 Steps (LLS), 12 Steps (TS) (rac)
Trotta 2015, 11 Steps (LLS), 14 Steps (TS) (rac)

Oridamycin B, R[1] = CO$_2$H, R[2] = CH$_2$OH
Li 2015, 14 Steps (LLS), 16 Steps (TS) (rac)
Trotta 2015, 13 Steps (LLS), 16 Steps (TS) (rac)

Xiamycin A, R[1] = Me, R[2] = CO$_2$H
Baran 2014, 14 Steps (LLS), 14 Steps (TS)
Li 2015, 9 Steps (LLS), 12 Steps (TS)
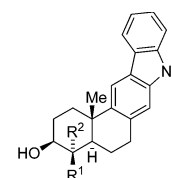
Oridamycin A
Now 7 Steps (LLS), 7 Steps (TS)

Triptoquinone B, R[1] = R[2] = O
Shishido 1993, 15 Steps (LLS), 15 Steps (TS) (rac)
Shishido 1997, 19 Steps (LLS), 19 Steps (TS)

Triptoquinone C, R[1] = OH, R[2] = H
Shishido 1993, 14 Steps (LLS), 14 Steps (TS) (rac)
Shishido 1997, 18 Steps (LLS), 18 Steps (TS)
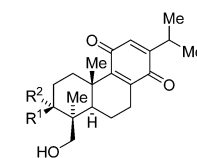
Triptoquinone B
Now 8 Steps (LLS), 11 Steps (TS)
Triptoquinone C
Now 7 Steps (LLS), 10 Steps (TS)

Iresin, 7,8-didehydro
Li 2015, 26 Steps (LLS), 27 Steps (TS)

Isoiresin, 8,9-didehydro
Pelletier 1968, 24 Steps (LLS), 24 Steps (TS) (rac)
Li 2015, 27 Steps (LLS), 28 Steps (TS)
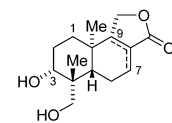
Isoiresin, 8,9-didehydro
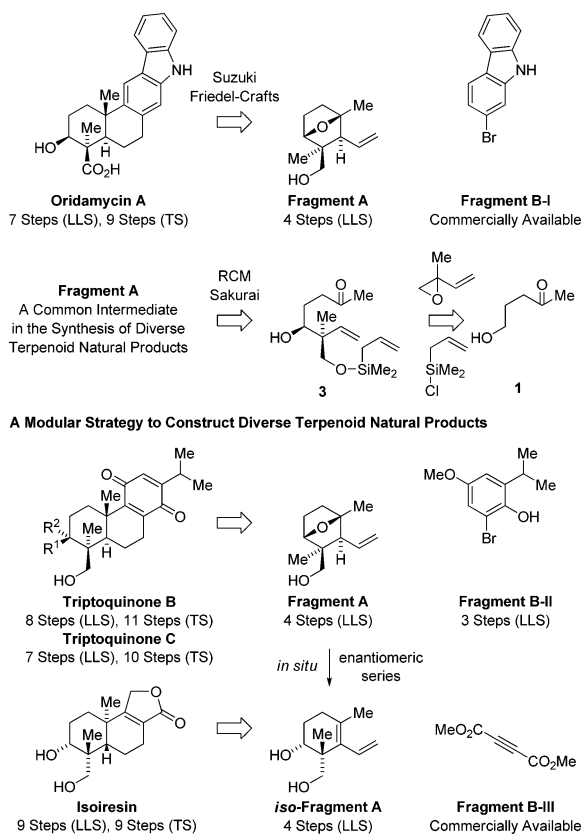Now 9 Steps (LLS), 9 Steps (TS)

Figure 1. Oridamycin A, triptoquinones B and C, and isoiresin and summary of prior total syntheses. For graphical summaries of prior total syntheses, see Supporting Information. LLS = longest linear sequence; TS = total steps.

quinones B and C, respectively. For isoiresin, Diels−Alder cycloaddition with *iso*-Fragment **A** and dimethyl acetylene dicarboxylate represents an alternative to Friedel−Crafts cyclization. Fragment **A**, the common intermediate *en route* to each natural product, is prepared in 4 steps through *anti*-diastereo- and enantioselective *tert*-(hydroxy)prenylation[5] of commercially available alcohol **1** followed by ring-closing metathesis[12] and intramolecular Sakurai allylation.[13] Sakurai allylation, when conducted under more forcing conditions, converts Fragment **A** to *iso*-Fragment **A**. Fragments **B-I**, **B-II**, and **B-III** symbolize the diversity of structural components that may be applied in this strategy, which serves as a convergent corridor to numerous members of the terpenoid class.

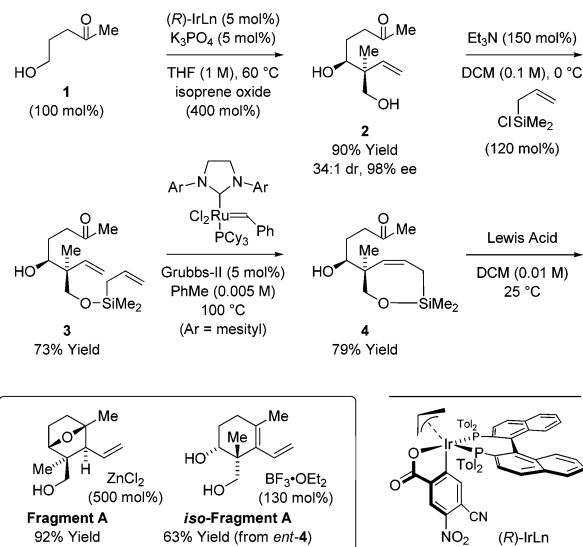## Scheme 1. Modular Retrosynthetic Analysis of Oridamycin A, Triptoquinones B and C, and Isoiresin

Scheme 2. Synthesis of Fragment A via *anti*-Diastereo- and Enantioselective Alcohol C—H *tert*-(Hydroxy)prenylation[a]

[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Scheme 3. Total Synthesis of Oridamycin A[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.
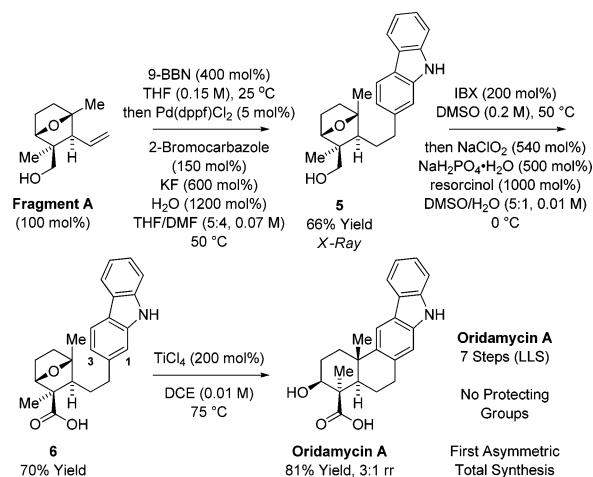
The synthesis of Fragment **A**, the common intermediate in the total synthesis of oridamycin A, triptoquinones B and C, and isoiresin is accomplished in only four steps (Scheme 2). The commercially available alcohol **1** is exposed to isoprene oxide in the presence of the π-allyliridium *C,O*-benzoate complex derived from 4-CN-3-NO$_2$-benzoic acid and (*R*)-Tol-BINAP in THF at 60 °C. The desired product of *anti*-diastereo- and enantioselective *tert*-(hydroxy)prenylation **2** is formed in 90% yield with remarkable *anti*-diastereoselectivity (34:1) and enantioselectivity (98% ee). Compound **2** exists in equilibrium with the 5-membered lactol and upon exposure to acid forms a cyclic ketal (not shown). Hence, chromatographic isolation required pretreatment of the silica gel with triethylamine. Exposure of **2** to allyldimethylsilyl chloride results in chemoselective functionalization of the primary neopentyl alcohol to provide silyl ether **3** in 73% yield, which upon ring-closing metathesis delivers the cyclic allylsilane **4**.[12] Compounds **3** and **4** exist in equilibrium with their 5-membered lactols, suggesting the [2.2.1]oxabicycle Fragment **A** may be formed upon intramolecular Sakurai allylation by way of an endocyclic oxacarbenium ion.[13] Indeed, exposure of allylsilane **4** to ZnCl$_2$ provides Fragment **A** as a single diastereomer in 92% yield. Using a stronger Lewis acid, BF$_3$·OEt$_2$, Fragment **A** eliminates *in situ* to *iso*-Fragment **A** in 63% yield.

Acquisition of Fragment **A** sets the stage for the synthesis of oridamycin A and triptoquinones B and C. Construction of oridamycin A was readily accomplished as follows (Scheme 3). Suzuki cross-coupling[14] of Fragment **A** with 2-bromocarbazole, Fragment **B-I**, was conducted by way of the alkyl 9-BBN derivative using KF as base.[15] The desired product of cross-coupling **5** was obtained in 66% isolated yield. Recognizing that

the oxidation of primary alcohols to aldehydes using IBX[16] and the Pinnick oxidation[17] of aldehydes to carboxylic acids can both be conducted in DMSO solvent,[18] a direct one-pot conversion of the primary alcohol **5** to the carboxylic acid **6** was developed. Friedel—Crafts cyclization[19] of carboxylic acid **6** would complete the synthesis of oridamycin A. Here, numerous Lewis acids and Brønsted acids were evaluated. In most cases, cyclization occurred in good yield; however, regioselectivity for the carbazole 1- vs 3-position was problematic. Optimal results were obtained using TiCl$_4$, which gave the product of Friedel—Crafts cyclization in 81% yield as a 3:1 mixture of regioisomers favoring oridamycin A. The present route to oridamycin A, which is protecting-group-free,[20] is the most concise total synthesis and the first asymmetric total synthesis of this natural product.
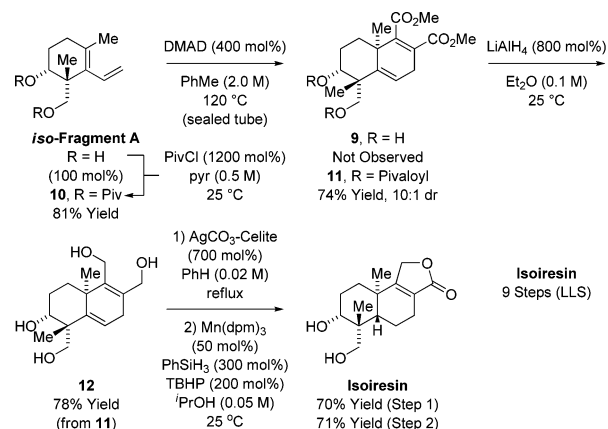
Scheme 4. Total Synthesis of Triptoquinones B and C[a]
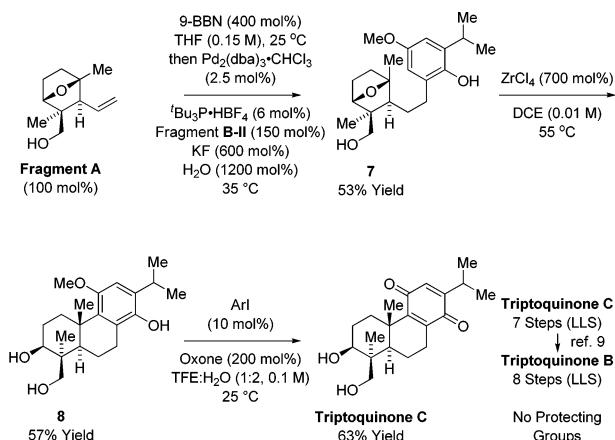
Scheme 5. Total Synthesis of Isoiresin[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details. ArI = 4-I-PhOCH$_2$CO$_2$H.

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

The conversion of Fragment **A** to triptoquinones B and C illustrates the modularity and generality of this convergent approach to terpenoid construction (Scheme 4). Suzuki cross-coupling[14,15] of Fragment **A** with Fragment **B-II** was accomplished in 53% yield using the palladium catalyst modified by tri-*tert*-butylphosphine.[21] Exposure of the Suzuki coupling product **7** to ZrCl$_4$ resulted in Friedel−Crafts cyclization to furnish the tricyclic compound **8** in 57% yield, which upon treatment with 4-iodophenoxyacetic acid in the presence of Oxone delivered triptoquinone C,[22] representing a formal synthesis of triptoquinone B.[9]

To further demonstrate the flexibility of the present approach to terpenoid construction, the total synthesis of isoiresin was undertaken using a complementary strategy (Scheme 5). *Iso*-Fragment **A** was heated in the presence of dimethyl acetylene dicarboxylate, Fragment **B-III**; however, the desired product of [4+2] cycloaddition **9** was not formed.[23] For the corresponding *bis*-acetate and *bis*-isobutyrate derivatives, the desired cyclo-adducts were generated in good yield with diastereoselectivities of 2.5:1 and 4.5:1, respectively. These data led us to investigate the cycloaddition of the *bis*-pivalate **10**, which delivered the product of cycloaddition **11** in 74% yield as a 10:1 mixture of diastereomers. Exposure of the tetraester **11** to LiAlH$_4$ provided the tetraol **12** in 78% yield. Finally, oxidative lactonization of the 1,4-ene-diol moiety[11b] in the presence of the saturated 1,3-diol followed by chemoselective Shenvi reduction of the less substituted olefin converted tetraol **12** to isoiresin.[24]

In summary, a modular, convergent, and step-economic strategy for terpenoid construction beyond cascade polycycliza-tions has been defined, as illustrated by the total synthesis of oridamycin A, triptoquinones B and C, and isoiresin from a common precursor. Our strategy is uniquely enabled by a catalytic method for primary alcohol C−H *tert*-(hydroxy)-prenylation that forms an all-carbon quaternary center with excellent control of diastereo- and enantioselectivity. In particular, alcohol C−H *tert*-(hydroxy)prenylation facilitates axial placement of the oxygenated A-ring methyl group (CH$_2$OH or CO$_2$R), which is difficult to achieve through classical cascade polycyclization.[25] The effectiveness of this protecting-group free strategy for convergent terpenoid construction is borne out by the fact that each natural product

is now prepared in significantly fewer steps than in any prior approach. Future studies will focus on the development and application of related catalytic methods for C−C bond formation that transcend use of stoichiometric organometallic reagents.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08902.

> Experimental procedures and spectral data for all new compounds; single-crystal X-ray diffraction data corresponding to compound **5** (PDF)

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Notes
The authors declare no competing financial interest.

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