

Synthesis of the Cytotrienin A Core via Metal Catalyzed C—C Coupling

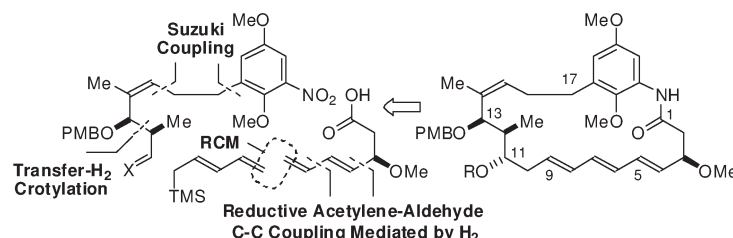
Michael Rössle, David J. Del Valle, and Michael J. Krische*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin,
Texas 78712, United States

mkrische@mail.utexas.edu

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ABSTRACT



A synthetic approach to the C17-benzene ansamycins via metal catalyzed C—C coupling is described. Key bond formations include direct iridium catalyzed carbonyl crotylation from the alcohol oxidation level followed by chelation-controlled Sakurai–Seyferth dienylation to form the stereotriad, which is attached to the arene via Suzuki cross-coupling. The diene-containing carboxylic acid is prepared using rhodium catalyzed acetylene-aldehyde reductive C—C coupling mediated by gaseous hydrogen. Finally, ring-closing metathesis delivers the cytotrienin core.

Beginning with the discovery of the antibacterial rifamycin B, ansamycin antibiotics continue to evoke interest as antibiotic and antineoplastic agents.¹ An important ansamycin subclass is represented by the ansatrienins, which are classified as triene-containing C17-benzene ansamycins. Members of this subclass, which are produced from various *Streptomyces* and *Bacillus* species, include

the mycotrienins and mycotrienols,² the trienomycins,³ and the cytotrienins (Figure 1).⁴ Whereas the mycotrienins exhibit potent antifungal activity,^{2d,e} the trienomycins and cytotrienins display antineoplastic properties.^{3a,5} For

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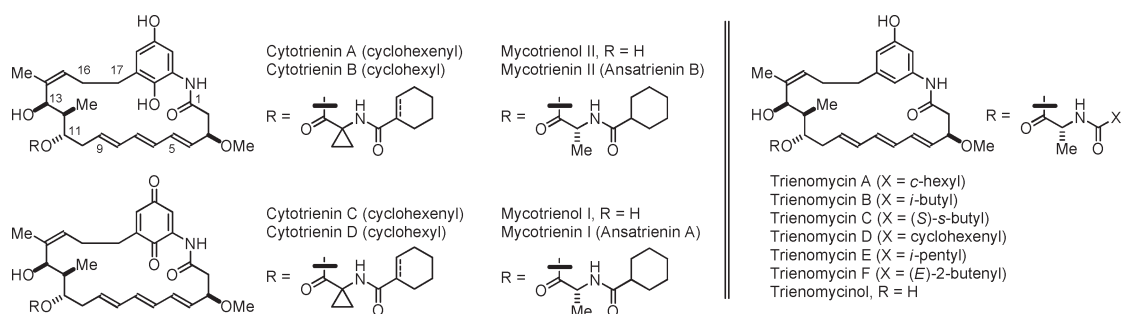
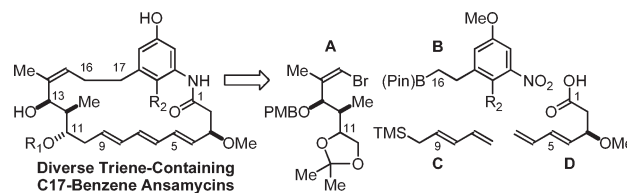


Figure 1. Representative ansatrienins: C17-benzene triene-ansamycin antibiotics.

example, cytotrienin A induces apoptosis in human acute promyelocytic leukemia HL-60 cells ($ED_{50} = 7.7$ nM).^{5c} Following their stereochemical assignment,⁶ total syntheses of trienomycins A and F and thiazinotrienomycin E were reported by Smith,^{7a–c} total syntheses of mycotrienol I and mycotrienin I were reported by Panek,^{7d,e} and a total synthesis of cytotrienin A was reported by Hayashi.^{7f} Finally, Kirschning and Panek reported syntheses of the ansatrienol and cytotrienin cores, respectively.⁸ Here, we report initial efforts toward the development of a synthetic approach to triene-containing C17-benzene ansamycins featuring C–C bond forming hydrogenations and transfer hydrogenations developed in our laboratory.⁹

Retrosynthetically, it was envisioned that diverse C17-benzene ansamycins may be accessed through modular assembly of fragments **A–D**. Specifically, Suzuki cross-coupling of vinyl bromide **A** and the organoboron building block **B** would deliver an arene-containing C11–C17 substructure. Chelation-controlled pentadienylation of the latent C11-aldehyde employing reagent **C** followed by reduction of the nitroarene and amidation of the resulting aniline with carboxylic acid **D** would provide a *bis*(diene), which upon macrocyclization *via* ruthenium catalyzed ring

Scheme 1. Retrosynthetic Analysis of C17-Benzene Triene-Ansamycins *via* Metal Catalyzed C–C Coupling



closing metathesis, as established by Panek,^{8b} would deliver the C17-benzene triene-ansamycin core (Scheme 1).

Synthesis of fragment **A**, which embodies the characteristic C17-benzene ansamycin stereotriad, begins with direct carbonyl crotylation of allylic alcohol **1a**¹⁰ mediated by α -methyl allyl acetate **1b** under the conditions of iridium catalyzed transfer hydrogenation.¹¹ High levels of *anti*-diastereo- and enantioselectivity are obtained using the isolated *ortho*-cyclometalated iridium *C,O*-benzoate precatalyst modified by (*S*)-SEGPHOS. As efforts toward corresponding *syn*-diastereoselective processes are underway,^{11d} the present first-generation synthesis requires conversion of the *anti*-adduct to the *syn*-diastereomer *via* Mitsunobu inversion employing *p*-nitrobenzoic acid¹² to deliver the crystalline *p*-nitrobenzoate **3**. Saponification of **3** followed by Williamson ether synthesis provides the *p*-methoxybenzyl ether **5**. Catalytic dihydroxylation to furnish **6** followed by conversion to the acetonide completes the synthesis of fragment **A** (Scheme 2).

The synthesis of fragment **B** begins with the Suzuki–Molander coupling of 1-bromo-2,5-dimethoxy-3-nitrobenzene with potassium ethenyltrifluoroborate.¹³ Hydroboration of the resulting vinylarene under standard conditions employing 9-BBN occurred regioselectively, but subsequent Suzuki coupling to produce **7** was problematic. For this reason, Miyaura’s method for iridium catalyzed

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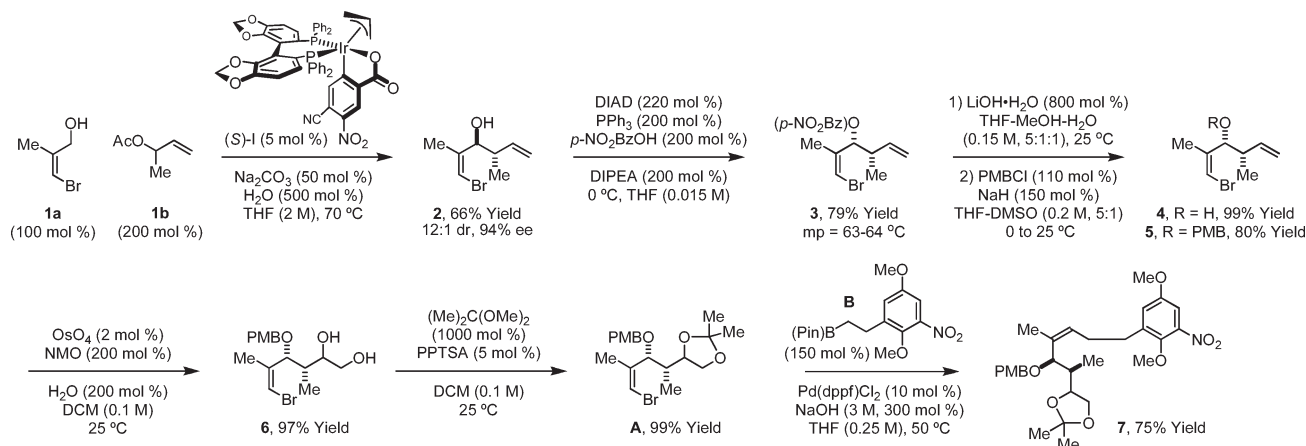
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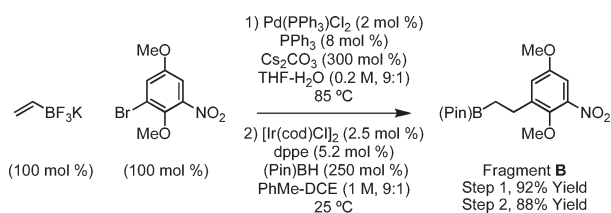
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Scheme 2. Synthesis of the Stereotriad-Containing Fragment **A** and Suzuki Cross-Coupling with Fragment **B**^a



^a See Supporting Information for detailed experimental procedures.

Scheme 3. Synthesis of Fragment **B**^a



^a See Supporting Information for detailed experimental procedures.

hydroboration employing pinacol borane was used, which delivered fragment **B** in a regioselective fashion (Scheme 3).¹⁴

The Suzuki coupling of fragments **A** and **B** was especially challenging. However, after screening numerous palladium sources and phosphine ligands, a remarkably simple protocol was identified, in which fragments **A** and **B** were exposed to Pd(dppf)Cl₂ in the presence of sodium hydroxide to furnish the product of C–C coupling **7** in 75% isolated yield (Scheme 2).

At this point, elaboration of **7** to the cytotrienin core was set as an initial goal of our first-generation synthetic approach to the C17-benzene triene-ansamycins. Toward this end, exposure of **7** to periodic acid in ethyl acetate solvent directly provides aldehyde **8**,¹⁵ which was subjected immediately to conditions for chelation-controlled¹⁶ pentadienylation.¹⁷ Gratifyingly, the desired adduct **9** was formed in a stereoselective fashion. To install the cytotrienin side chain, Hayashi's protocol was employed.^{7f} Specifically, alcohol **9** was converted to the α -azido-cyclopropane carboxylic ester **10**. Reduction of the azide followed by

acylation of the resulting amine **11** using cyclohexene carboxylic acid delivers **12** (Scheme 4).

Elaboration of **12** to the cytotrienin A core requires preparation of diene-containing carboxylic acid **D**. Previously, carboxylic acid **D** was produced in 12 steps in 16% overall yield.^{7f} Hydrogen-mediated C–C coupling of acetylene¹⁸ to the *p*-toluenesulfonate of hydroxy acetaldehyde delivers the indicated product of (*Z*)-butadienylation, which upon *O*-methylation and isomerization of the diene¹⁹ provides the indicated (*E*)-homoallylic sulfonate. Displacement of the *p*-toluenesulfonate by cyanide and, finally, hydrolysis of the resulting nitrile furnishes carboxylic acid **D** in 7 steps from allyl alcohol in 32% overall yield (Scheme 5). With carboxylic acid **D** in hand, compound **12** is transformed to *bis*(diene) **13** via reduction of the nitroarene employing NaBH₂S₃²⁰ followed by acylation of the resulting aniline (Scheme 4).

Initial exploration of the ruthenium catalyzed ring-closing metathesis (RCM) reaction of *bis*(diene) **13** and related model systems revealed exceptional sensitivity to both the catalyst and the substituent at C11. For example, in model studies involving the corresponding C11 TBS-ether of *bis*(diene) **13**, RCM using the Grubbs–Hoveyda-II catalyst occurred to deliver the diene product exclusively. Eventually, it was found that diene formation is suppressed for *O*-acyl derivatives at C11 and, gratifyingly, the actual cytotrienin A side chain proved to be ideal. Thus, using the indenylidene analogue of the first generation Grubb's metathesis catalyst,²¹ *bis*(diene) **13** is converted to the cytotrienin A core in 43% yield. Difficulties encountered

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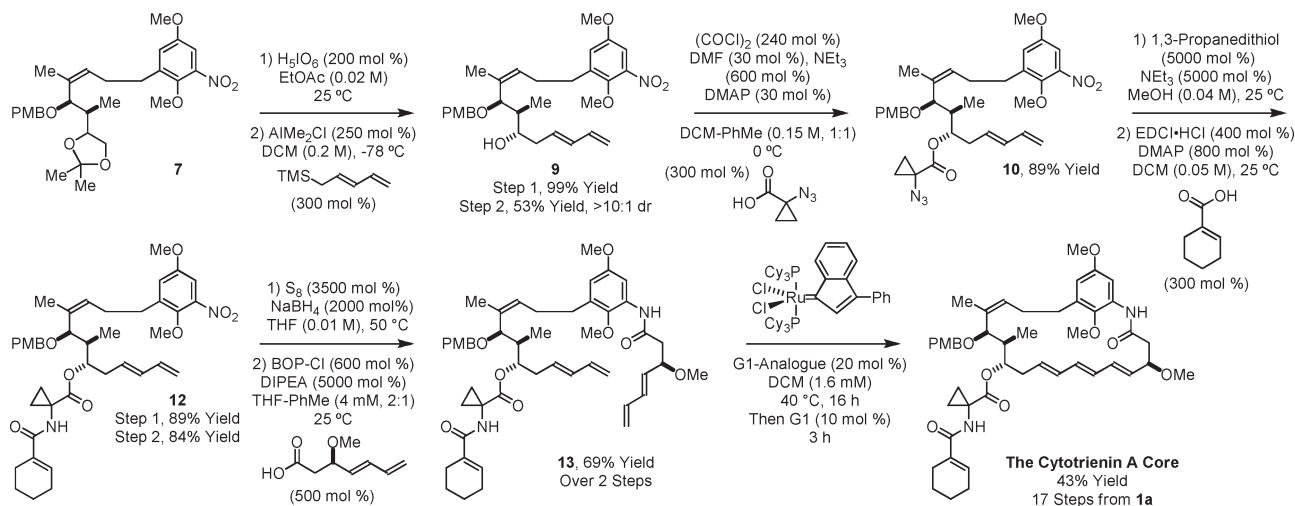
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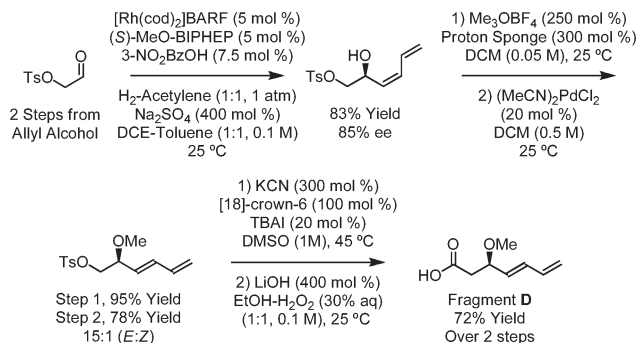
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Scheme 4. Elaboration of Suzuki Cross-Coupling Product **7** to the Cytotrienin Core^a



^a See Supporting Information for detailed experimental procedures.

Scheme 5. Synthesis of Diene-Containing Carboxylic Acid **D** via Hydrogen-Mediated C–C Coupling^a



^a See Supporting Information for detailed experimental procedures.

in the removal of the methyl ether functionality prevented conversion of this material to the natural product.

In summary, we report a first-generation approach to the C17-benzene triene-ansamycins, as demonstrated by the synthesis of the cytotrienin A core in 17 steps from alcohol **1a** (longest linear sequence). This study serves as a prelude to second-generation routes of greater step economy, which will incorporate *syn*-diastereo- and enantioselective carbonyl crotylation of alcohol **1a** and the use of phenolic protecting groups amenable to late-stage cleavage.

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Supporting Information Available. Characterization data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS, $[\alpha]$). This material is available free of charge via the Internet at <http://pubs.acs.org>.