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Synthesis of the Cytotrienin A Core *via* Metal Catalyzed C-C Coupling

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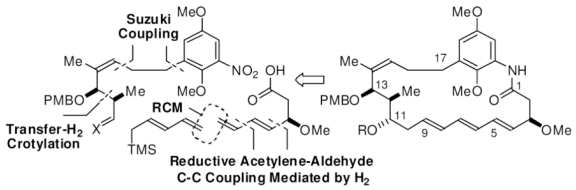
Abstract



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, RCM 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 Steptomyces and Bacillus species, include the mycotrienins and mycotrienols,[2] the trienomycins[3] and the cytotrienins (Figure 1).4 Whereas the mycotrienins exhibit potent anti-fungal activity,2d,e the trienomycins and cytotrienins display antineoplastic properties. 3a,[5] For example, cytotrienin A induces apoptosis in human acute promyelocytic leukemia HL-60 cells (ED50 = 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 Panek7d,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

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

aniline with carboxylic acid **D** provides a *bis*(diene), which upon macrocyclization *via* ruthenium catalyzed ring 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*-cyclometallated 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 acid[12] 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 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 $Pd(dppf)Cl_2$ 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-controlled[16] 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 acetylene[18] to the *p*-toluenesulfonate of hydroxy acetaldehyde delivers the indicated product of (*Z*)-butadienylation, which upon *O*-methylation and isomerization of the diene[19] provide the indicated (*E*)-homoallylic sulfonate. Displacement of the *p*-toluenesulfonate by cyanide and, finally, hydrolysis of the resulting nitrile delivers 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 $NaBH_2S_3$[20] followed by acylation of the resulting aniline (Scheme 4).

Initial exploration of the ruthenium catalyzed 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 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 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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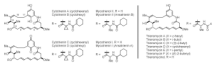
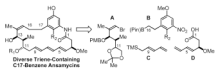
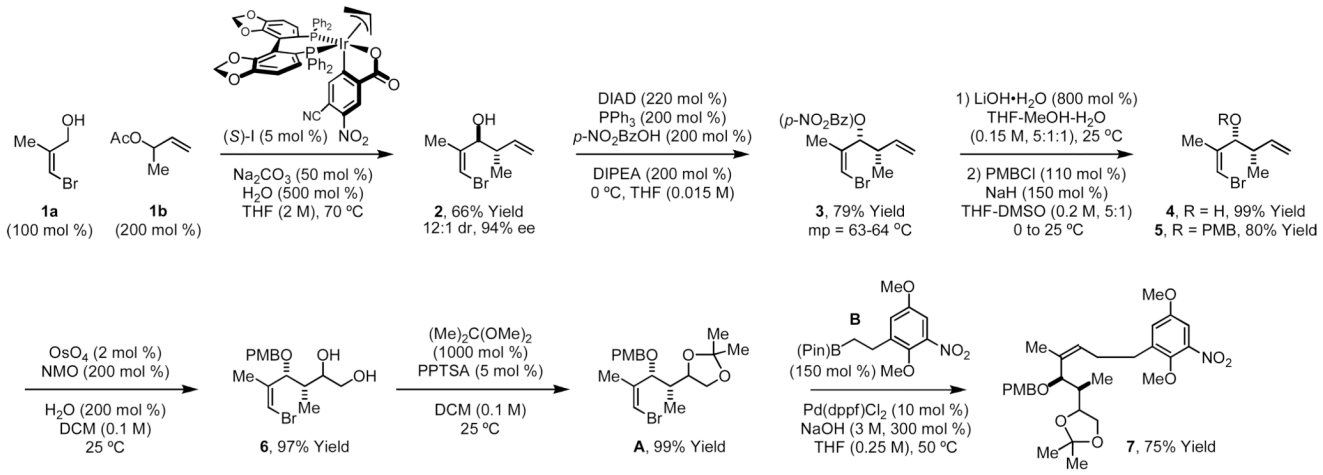


Figure 1.
Representative ansatrienins: C17-benzene triene-ansamycin antibiotics.



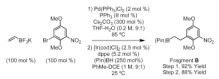
Scheme 1.
Retrosynthetic analysis of C17-benzene trieneansamycins *via* metal catalyzed C-C coupling.



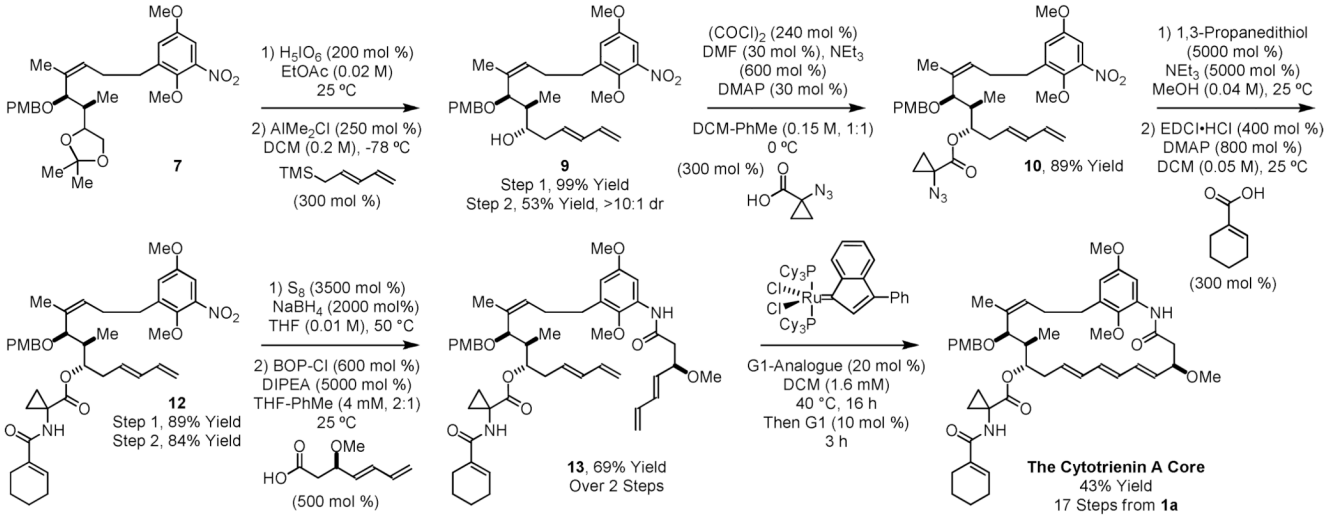
Scheme 2.

Synthesis of the stereotriad-containing fragment **A** and Suzuki cross-coupling with fragment **B**.a

[a]See Supporting Information for detailed experimental procedures.



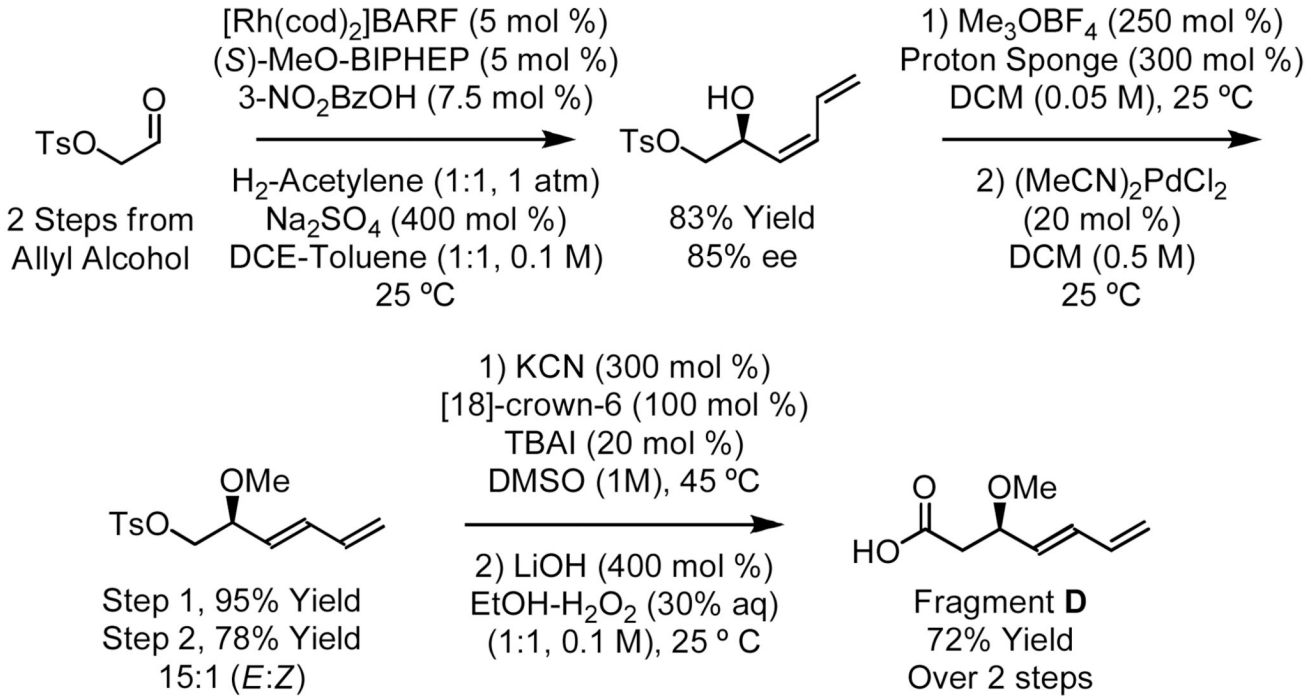
Scheme 3.
Synthesis of fragment **B**.a
[a]See Supporting Information for detailed experimental procedures.



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.