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

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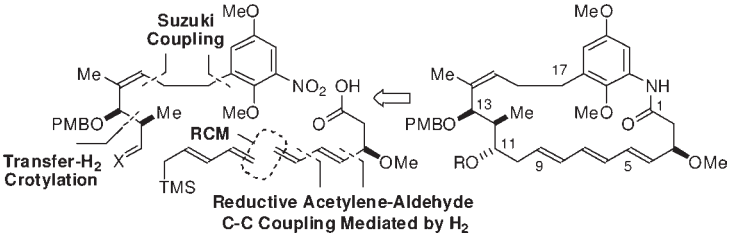
ABSTRACT



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, 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

(1) For selected reviews on ansamycin natural products, see: (a) Wrona, I. E.; Agouridas, V.; Panek, J. S. *C. R. Acad. Sci., Paris* **2008**, *11*, 1483. (b) Funayama, S.; Cordell, G. A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 2000; Vol. 23, pp 51−106.

(2) For isolation of mycotrienols I and II and mycotrienins I and II (ansatrienins A and B), see: (a) Weber, W.; Zuehner, H.; Damberg, M.; Russ, P.; Zeeck, A. *Zbl. Bakt. Hyg., Abt. Orig. C2* **1981**, 122. (b) Zeeck, A.; Damberg, M.; Russ, P. *Tetrahedron Lett.* **1982**, *23*, 59. (c) Sugita, M.; Furihata, K.; Seto, H.; Otake, N.; Sasaki, T. *Agric. Biol. Chem.* **1982**, *46*, 1111. (d) Sugita, M.; Natori, Y.; Sasaki, T.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1460. (e) Sugita, M.; Sasaki, T.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1467. (f) Sugita, M.; Natori, Y.; Sueda, N.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1474. (g) Sugita, M.; Hiramoto, S.; Ando, C.; Sasaki, T.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 799.

(3) For isolation of trienomycins A−F, see: (a) Umezawa, I.; Funayama, S.; Okada, K.; Iwasaki, K.; Satoh, J.; Masuda, K.; Komiyama, K. *J. Antibiot.* **1985**, *38*, 699. (b) Hiramoto, S.; Sugita, M.; Ando, C.; Sasaki, T.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 1103. (c) Funayama, S.; Okada, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1107. (d) Funayama, S.; Okada, K.; Iwasaki, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1677. (e) Nomoto, H.; Katsumata, S.; Takahashi, K.; Funayama, S.; Komiyama, K.; Umezawa, I.; Omura, S. *J. Antibiot.* **1989**, *42*, 1677. (f) Smith, A. B., III; Wood, J. L.; Gould, A. E.; Omura, S.; Komiyama, K. *Tetrahedron Lett.* **1991**, *32*, 1627.

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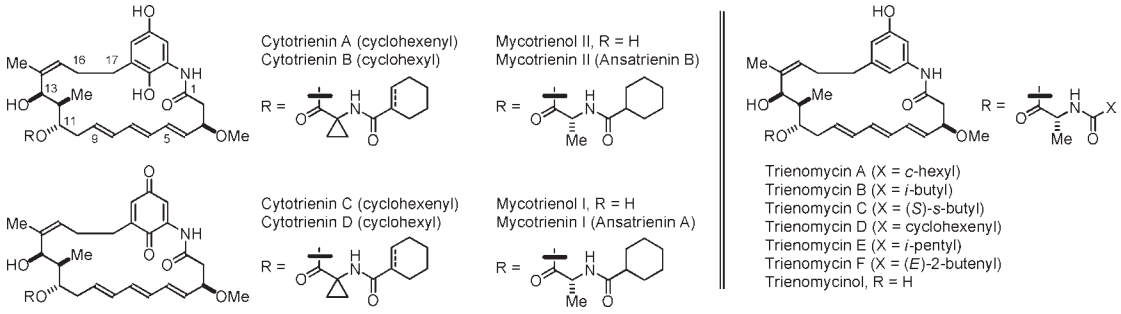
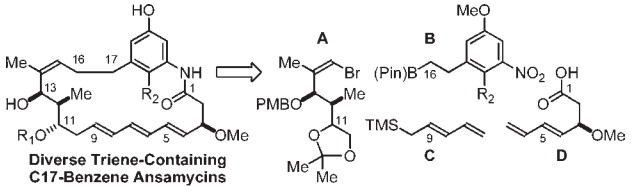


Figure 1. Representative ansatrienins: C17-benzene triene-ansamycin antibiotics.

example, cytotrienin A induces apoptosis in human acute promyelocytic leukemia HL-60 cells (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 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 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

(8) For syntheses of the ansatrienol and cytotrienin cores, see: (a) Kashin, D.; Meyer, A.; Wittenberg, R.; Schoning, K.-U.; Kamlage, S.; Kirschning, A. *Synthesis* **2007**, 304. (b) Evano, G.; Schaus, J. V.; Panek, J. S. *Org. Lett.* **2004**, *6*, 525.

(9) For selected reviews on C−C bond forming hydrogenation and transfer hydrogenation, see: (a) Ngai, M.-Y.; Kong, J. R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394. (c) Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichimica Acta* **2008**, *41*, 95. (d) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102. (e) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (f) Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Commun.* **2009**, 7278. (g) Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011**, *43*, 107.

(10) Alcohol **1a** was prepared using a variation of the literature procedure: Fang, G.-H.; Yan, J.-Z.; Yang, J.; Deng, M.-Z. *Synthesis* **2006**, 1148. Experimental details are included in the Supporting Information.

(11) For enantioselective iridium catalyzed carbonyl crotylation from the alcohol oxidation level, see: (a) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (b) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313. (c) Bechem, B.; Patman, R. L.; Hashmi, A. S. K.; Krische, M. J. *J. Org. Chem.* **2010**, *75*, 1795. (d) Zbieg, J. R.; Fukuzumi, T. *Adv. Synth. Catal.* **2010**, *352*, 2416. (e) Han, S. B.; Hassan, A.; Kim, I.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15559.

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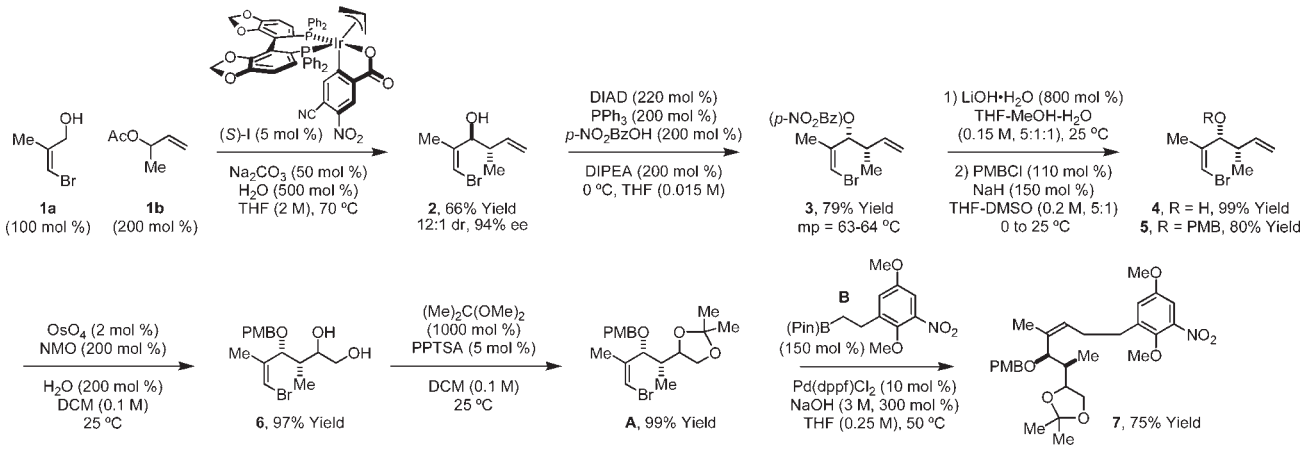
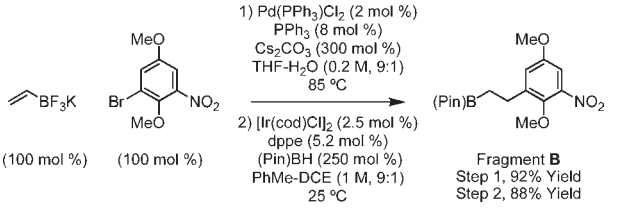
Scheme 2. Synthesis of the Stereotriad-Containing Fragment **A** and Suzuki Cross-Coupling with Fragment **B**[a]



[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 $Pd(dppf)Cl_2$ 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] 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 $NaBH_2S_3$[20] 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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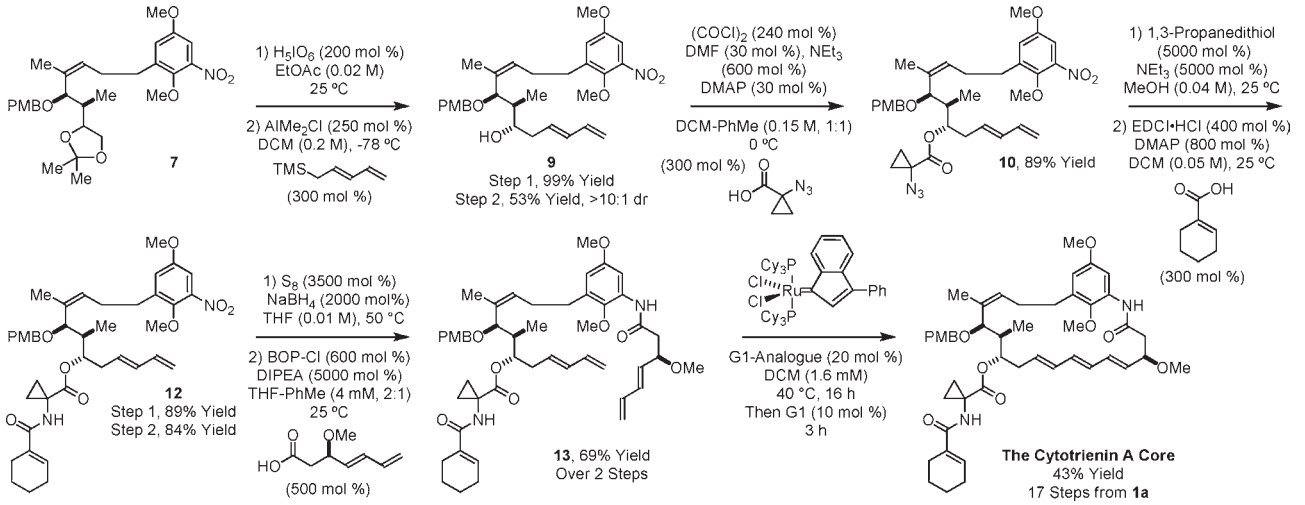
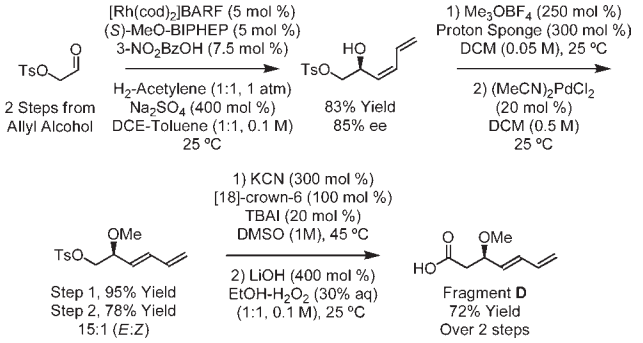
Scheme 4. Elaboration of Suzuki Cross-Coupling Product **7** to the Cytotrienin Core[a]



[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 (^{1}H NMR, ^{13}C NMR, IR, HRMS, [α]). This material is available free of charge via the Internet at http://pubs.acs.org.