

Total Synthesis of (+)-Trienomycins A and F via C–C Bond-Forming Hydrogenation and Transfer Hydrogenation

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Supporting Information

ABSTRACT: The triene-containing C17-benzene ansamycins trienomycins A and F were prepared in 16 steps (longest linear sequence, LLS) and 28 total steps. The C11–C13 stereotriad was generated via enantioselective Ru-catalyzed alcohol CH syn crotylation followed by chelation-controlled carbonyl dienylation. Enantioselective Rh-catalyzed acetylene–aldehyde reductive coupling mediated by gaseous H₂ was used to form a diene that ultimately was subjected to diene–diene ring closing metathesis to form the macrocycle. The present approach is 14 steps shorter (LLS) than the prior syntheses of trienomycins A and F, and 8 steps shorter than any prior synthesis of a triene-containing C17-benzene ansamycin.

Roughly 20% of the top-selling small-molecule drugs are polyketides derived from soil bacteria,^{1,2} and it is estimated that polyketides are 5 times more likely to possess drug activity compared to other classes of natural products.³ Despite the significance of polyketides, less than 5% of the soil bacteria from which they derive are amenable to culture.⁴ Hence, as methods for bacterial culture improve, it is anticipated that polyketides will become even more important to human medicine. Among polyketides, the ansamycins have emerged as important antibiotic and anti-neoplastic agents.⁵ The first ansamycins, the rifamycins, were discovered in the late 1950s in soil samples taken from the south of France.⁶ These compounds were largely responsible for vanquishing drug-resistant tuberculosis in the 1960s and were forerunners of what is now a broad class of medically relevant compounds.⁵ An important ansamycin subclass includes the triene-containing C17-benzene ansamycins or “ansatrienins”.^{7–9} This subclass emanates from different *Streptomyces* and *Bacillus* species and encompasses the mycotrienins/mycotrienols,⁷ the trienomycins,⁸ and the cytотrienins (Figure 1).⁹ While the mycotrienins display antifungal properties,^{7d,e} the trienomycins and cytотrienins exhibit anti-neoplastic activity.^{8a,9b,10} Elegant studies conducted in the Smith laboratory led to the stereochemical assignment of the trienomycins and mycotrienins¹¹ as well as total syntheses of trienomycins A and F and thiazinotrienomycin E.^{12a–d} Subsequently, Panek reported total syntheses of mycotrienol I and mycotrienin I,^{12e,f} and Hayashi reported a total synthesis of cytотrienin A.^{12g} Syntheses of the ansatrienol and cytотrienin cores were reported by Kirschning,^{13a} Panek,^{13b} and the present author.^{13c} Here, using hydrogen mediated C–C couplings developed in our laboratory,¹⁴ we report total syntheses of the triene-containing C17-benzene ansamycins, trienomycins A and

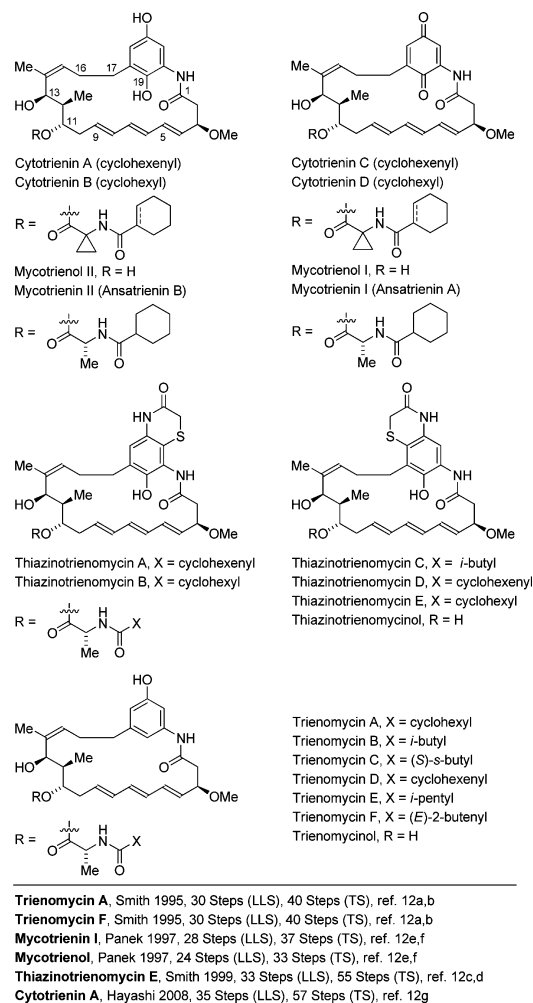


Figure 1. Triene-containing C17-benzene ansamycins and prior total syntheses. For graphical summaries of prior total syntheses, see the Supporting Information (SI). For total syntheses of other ansamycin family members, see the review literature.⁵ LLS = longest linear sequence; TS = total steps.

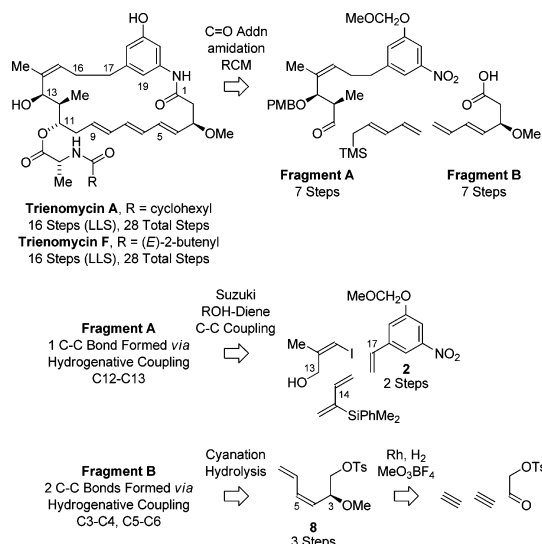
F. This approach represents the most concise route to any triene-containing C17-benzene ansamycin.

Our retrosynthetic analysis of trienomycins A and F invokes a convergent assembly of fragments A and B wherein (*E*)-

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trimethyl-2,4-pentadienylsilane¹⁵ serves as a linchpin through chelation-controlled aldehyde addition¹⁶ followed by diene–diene ring closing metathesis (RCM) (Scheme 1).^{13b} Fragment

Scheme 1. Retrosynthetic Analysis of Trienomycins A and F

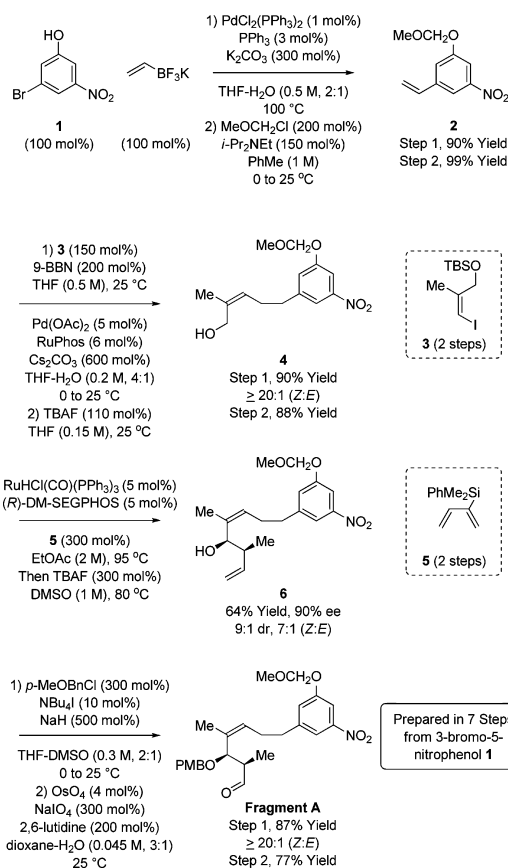


A is itself prepared using an enantio- and *syn*-diastereoselective Ru-catalyzed crotylation developed in our laboratory,¹⁷ which enables direct C–C coupling of the *Z*-configured trisubstituted allylic alcohol obtained via Suzuki reaction of (*Z*)-3-iodo-2-methyl-1-propenol and the indicated vinyl arene **2**. Fragment **B** is prepared in accordance with our previously described procedure involving C–C bond-forming hydrogenation of acetylene in the presence of the *p*-toluenesulfonate of hydroxyacetaldehyde.^{13c,18} The present syntheses of trienomycins **A** and **F** overcomes limitations evident in our prior work on the cytatrienin core pertaining to formation of the C11–C13 stereotriad, introduction of the side chain at C11, and late-stage protecting group cleavage.^{13c}

The synthesis of fragment **A** begins with successive Suzuki cross-couplings to form the C17–C18 and C15–C16 bonds (Scheme 2). First, Suzuki–Molander coupling of 3-bromo-5-nitrophenol (**1**) with potassium ethenyltrifluoroborate¹⁹ provides vinyl arene **2** after methoxymethyl (MOM) protection. Second, in a one-pot procedure, regioselective hydroboration of **2** using 9-borabicyclo[3.3.1]nonane (9-BBN) followed by *B*-alkyl Suzuki cross-coupling^{20,21} with (*Z*)-3-iodo-2-methyl-1-propenol *tert*-butyldimethylsilyl (TBS) ether (**3**)²² provides (*Z*)-allylic alcohol **4** as a single olefin stereoisomer. Direct redox-triggered *syn*-crotylation of **4** using silyl-substituted diene **5** as a crotyl donor^{17a} enables enantio- and diastereoselective formation of homoallylic alcohol **6**. Protection of the C13 alcohol as the *p*-methoxybenzyl (PMB) ether followed by oxidative cleavage of the terminal olefin using a modification of the Johnson–Lemieux protocol²³ provides aldehyde **Fragment A** in only seven steps from **1**.

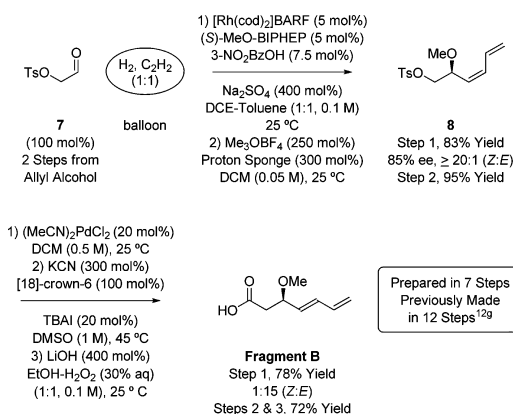
The carboxylic acid, **Fragment B**, was prepared previously in 12 steps in 16% overall yield.^{12g} Our approach to fragment **B** is accomplished in seven steps from allyl alcohol in 32% overall yield.^{13c} The synthesis begins with enantioselective H₂-mediated C–C coupling of acetylene to acetaldehyde derivative **7** to form the *Z*-butadienylation product,¹⁸ which upon treatment with Meerwein's reagent provides methyl ether **8** (Scheme 3). Pd-catalyzed diene isomerization²⁴ followed by substitution of the *p*-

Scheme 2. Synthesis of Fragment A via Ru-Catalyzed *syn*-Crotylation Employing Silyl-Substituted Diene **5**^a



^aIndicated yields are of materials isolated by silica gel chromatography. See the SI for experimental details.

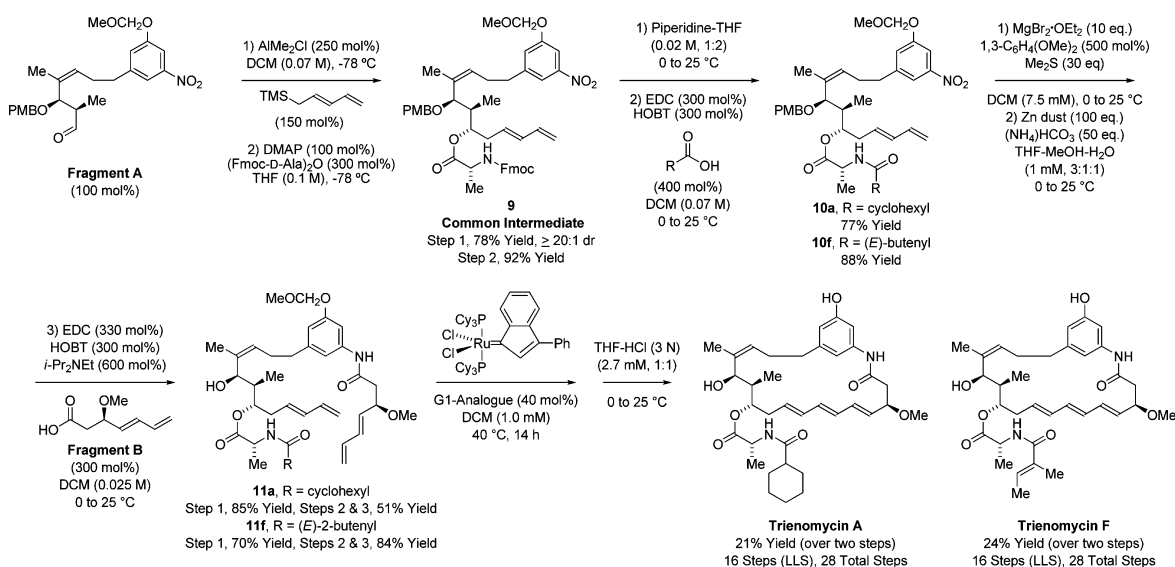
Scheme 3. Synthesis of Fragment B via Rh-Catalyzed Reductive C–C Coupling of Acetylene^a



^aIndicated yields are of materials isolated by silica gel chromatography. See the SI for experimental details.

toluenesulfonate by cyanide and, finally, peroxide-assisted hydrolysis of the resulting nitrile delivers fragment **B**. A remarkable feature of this sequence relates to the ability to engage aldehyde **7** in carbonyl *Z*-butadienylation without inducing epoxide formation through displacement of the vicinal *p*-toluenesulfonate.

To complete the syntheses of trienomycins **A** and **F**, fragment **A** is exposed to (*E*)-trimethyl-2,4-pentadienylsilane¹⁵ in the

Scheme 4. Union of Fragments A and B and Total Synthesis of Trienomycins A and F^a

^aIndicated yields are of materials isolated by silica gel chromatography. See the SI for experimental details.

presence of AlMe_2Cl to generate the product of chelation-controlled pentadienylation,¹⁶ which is followed by acylation with the symmetrical anhydride of *N*-Fmoc-D-alanine to provide **9** (Scheme 4). It was found that the major *syn* diastereomer of fragment A reacts more quickly than the corresponding *anti*-diastereomer, allowing the stereotriad of **9** to form as a single isomer as determined by ^1H NMR analysis.²⁵ Because different acyl moieties can be introduced at C11, **9** serves as a common intermediate in the syntheses of trienomycins A and F and potentially other triene-containing C17-benzene ansamycins. Treatment of **9** with piperidine followed by the indicated acids permits formation of amides **10a** and **10f**. Cleavage of the PMB ethers of **10a** and **10f** in the presence of the 1,3-diene moieties requires special conditions.²⁶ Subsequent reduction of the C20 nitro moieties and acylation of the resulting anilines with fragment B provides tetraenes **11a** and **11f**, respectively. Finally, diene–diene RCM to form the triene was explored.^{13b,c} With Grubbs' first- and second-generation catalysts and the Grubbs–Hoveyda-II catalyst, RCM occurs to form substantial quantities of undesired diene products (30–40%). The indenylidene analogue of the first-generation Grubbs metathesis catalyst²⁷ is more selective for triene formation, although modest yields are obtained, perhaps due to the lack of a conformational-biasing element in the form of a C19 substituent. Triene formation in this manner followed by removal of the MOM protecting group completes the total syntheses of trienomycins A and F in 16 steps (LLS). This sequence is 14 steps (LLS) shorter than the prior syntheses of trienomycins A and F,^{12a,b} and 8 steps shorter than any prior synthesis of a triene-containing C17-benzene ansamycin.

In summary, with the exception of eribulin, a truncated derivative of halichondrin,²⁸ all FDA-approved polyketides are prepared through fermentation or semisynthesis, as current synthetic methods cannot concisely address the preparation of such complex structures. Accordingly, our laboratory has devised a suite of catalytic methods for polyketide construction wherein the addition, exchange, or removal of hydrogen is accompanied by C–C bond formation.¹⁴ As illustrated by the present total syntheses of trienomycins A and F and prior total syntheses of roxaticin,^{29a} bryostatin 7,^{29b} 6-deoxyerythronolide B,^{29c} and

cyanolide A^{29d} as well as formal syntheses of rifamycin S and scytophycin C,^{29e} applications of our technology have availed the most concise routes to any member of these natural product families. Future studies will focus on the development of related catalytic processes that streamline syntheses by merging redox and C–C bond construction events.^{30,31}

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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