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

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Research Interests

- H₂-Mediated C-C Coupling
- Natural Product Synthesis
- Nucleophilic Catalysis
- Cat. Conj. Addition / Trapping
- Metal-Catalyzed [2+2] Cycloaddition
(+)-Trienomycins A and F

\[ R = \text{cyclohexyl (A) or (E)-2-butenyl (F)} \]
Retrosynthetic Analysis of (+)-Trienomycins A and F

R = cyclohexyl (A) or (E)-2-butenyl (F)
(+)-Trienomycins A and F

Fragment A

Fragment B

Retrosynthetic analysis of (+)-Trienomycins A and F

The Synthesis of Fragment A

1) PdCl₂(PPh₃)₂, PPh₃, K₂CO₃, 90%
2) MeOCH₂Cl, i-Pr₂NEt, 99%

1) 9-BBN, Pd(OAc)₂, RuPhos, Cs₂CO₃, 90%
2) TBAF, 88%

RuHCl(CO)(PPh₃)₃ (R)-DM-SegPhos, 64% yield, 90% ee, 9:1 dr, 7:1 (Z:E)

The Synthesis of Fragment B

**Fragment A**

\[
\text{MeOCH}_2\text{O} \quad \text{MeOCH}_2\text{O}
\]

1. \(\text{p-MeOBnCl},\ \text{NBu}_4^+,\ \text{NaH}\)  
   \(87\%\text{ yield}, \ 20:1\ (Z:E)\)

2. \(\text{OsO}_4,\ \text{NaO}_4,\ 2,6\)-Lutidine  
   \(77\%\)

**Fragment B**

\[
\text{TsO} \quad \text{TsO}
\]

1. \([\text{Rh}(\text{cod})_2]\text{BARF}\)  
   \((\text{S})\-\text{MeO-BiPHEP}\)  
   \(3\-\text{NO}_2\)-BzOH, \(\text{Na}_2\text{SO}_4\)  
   \(83\%\text{ yield}, \ 85\%\text{ ee}\)

2. \(\text{Me}_3\text{OBF}_4,\ \text{Proton Sponge}\)  
   \(95\%\)

3. \((\text{MeCN})_2\text{PdCl}_2,\ 78\%\)

4. \(\text{KCN},\ [18]\)-crown-6, TBAI

5. \(\text{LiOH},\ 72\%,\ 2\text{ steps}\)

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H₂ Mediated C-C Bond Coupling Reaction:


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1) NaHMDS, (EtO)₂POCl then t-BuLi, 84%
2) t-BuLi, ClCO₂Me, 93%

1) Me₂CuLi, 94%
2) DIBAL, 91%
3) MsCl, LiCl, 98%
4) NaI, acetone

Michael J. Krische:

- 16 Steps (14 steps shorter than the prior).
- The C11-C13 was Generated via Ru-catalyzed Alcohol CH syn Crotylation.
- Rh-Catalyzed Reductive Coupling Mediated by H₂.
- Ring Closing Metathesis Reaction.
John L. Wood:

\[ R = \text{cyclohexyl (A) or (E)-2-butanyl (F)} \]

\( (+)^{-}\)-Trienomycins A and F

- **The First** Formal Total Synthesis.
- **19** Steps.
Roughly 20% of the top-selling small-molecule drugs are polyketides derived from soil bacteria, and it is estimated that polyketides are 5 times more likely to possess drug activity compared to other classes of natural products. Despite the significance of polyketides, less than 5% of the soil bacteria from which they derive are amenable to culture. 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. The first ansamycins, the rifamycins, were discovered in the late 1950s in soil samples taken from the south of France. These compounds were largely responsible for vanquishing drug-resistant tuberculosis in the 1960s and were forerunners of what is now a broad class of medicinally relevant compounds. An important ansamycin subclass includes the triene-containing C17-benzene ansamycins. This subclass emanates from different Streptomyces and Bacillus species and encompasses the mycotrienins/mycotrienols, the trienomycins, and the cytotrienins. While the mycotrienins display antifungal properties, the trienomycins and cytotrienins exhibit antineoplastic activity.
Elegant studies conducted in the Smith laboratory led to the stereochemical assignment of the trienomycins and mycotrienins as well as total syntheses of trienomycins A and F. Subsequently, Panek reported total syntheses of mycotrienol I and mycotrienin I, and Hayashi reported a total synthesis of cytotrienin A. Syntheses of the ansatrienol and cytotrienin cores were reported by Kirschning, Panek, and the present author. Here, using hydrogen mediated C−C couplings developed in our laboratory, we report total syntheses of the triene-containing C17-benzene ansamycins, trienomycins A and F. This approach represents the most concise route to any trienecontaining C17-benzene ansamycin.
In summary, with the exception of eribulin, a truncated derivative of halichondrin, 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. As illustrated by the present total syntheses of trienomycins A and F and prior total syntheses of roxaticin, bryostatin 7, 6-deoxyerythronolide B, and cyanolide A as well as formal syntheses of rifamycin S and scytophycin C, 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.