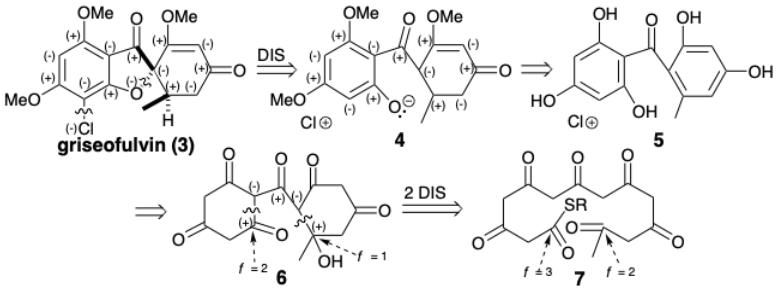
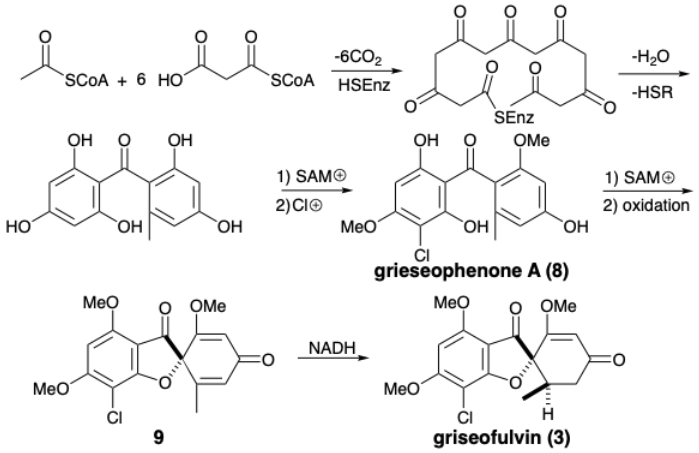
5.2: Griseofulvin

Polar reactivity analysis of griseofulvin (**3**) reveals dissonant circuits involving the chloro substituent and furan oxygen. A dislocation cleaving these dissonant circuits suggests an entirely consonant precursor **4** or the aromatic close relative **5**. This disconnection -- between a common atom, the spiro carbon, and a non common atom, the furan oxygen -- also leads to major topological simplification. Disconnection of the rings ring in **5** to generate an acyclic precursor must be preceded by conversion of ring C=C bonds into C-C bonds. Thus, addition of water or tautomerization gives a precursor **6** in which polar disconnection of C-C single bonds is feasible. The functionality level at the electrophilic centers in the acyclic precursor **7** suggested by this polar disconnection must be one unit higher than in the intermediate **6** if the cyclization of **6** is to yield **7** *directly*.

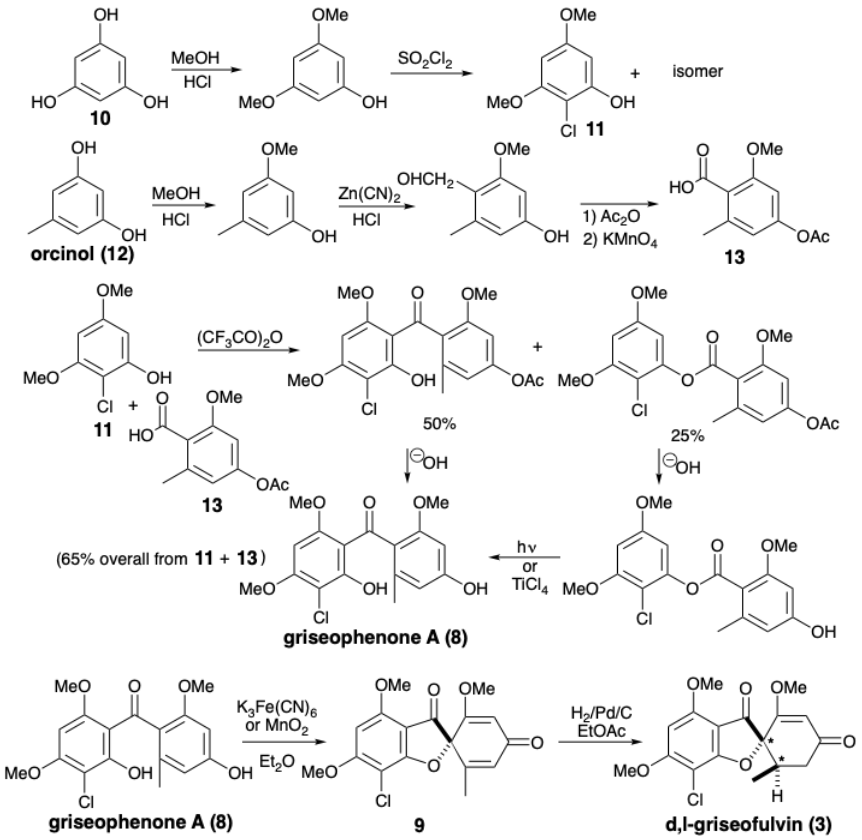


The biosynthesis of griseofulvin (**3**) illustrates the involvement of electrophilic aromatic substitution and oxidative coupling in the transformation of a poly-β-ketomethylene chain into a functionally and skeletally complex acetogenin. Thus, intramolecular aldol condensations of an enzyme- bound 3,5,7,9,11,13-hexaketohexadecanoic acid thioester followed by hydrolysis, O-methylation with S-adenosylmethionine (SAM) and electrophilic aromatic chlorination generates an intermediate, griseophenone A (**8**). A dissonant connection in the furan ring of griseofulvin is created by an oxidative coupling that generates dehydrogriseofulvin (**9**) from **8**. Stereo-selective reduction of **9** with NADH then delivers griseofulvin (**3**).



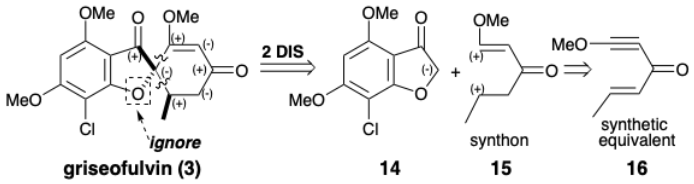
A Biomimetic Synthesis of Griseofulvin

A ferricyanide-induced oxidative coupling of griseophenone A (**8**) to dehydrogriseofulvin (**9**) with was exploited in a biomimetic total synthesis of racemic griseofulvin.[2] The symmetrical starting materials, phloroglucinol (**10**) and orcinol (**12**) were elaborated into the intermediates **11** and **13** by well precedented electrophilic aromatic substitutions. Acylation of **11** with **13** occurred mainly at carbon. The O-acylation product was readily rearranged to the C-acylation product, thus affording griseophenone A (**8**) in good overall yield. Conversion of **8** to d,l-griseofulvin (**3**) closely paralleled the biosyn-thetic pathway.

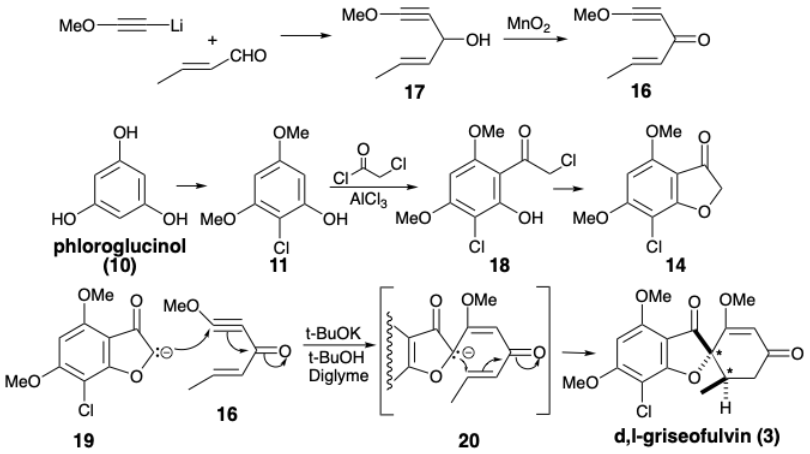


Polar Cyclohexenone Annelation Strategies for Griseofulvin

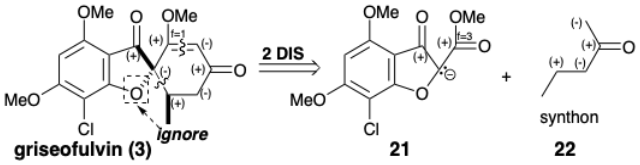
A strategy for the total synthesis of griseofulvin is suggested by a polar analysis that ignores the polar activation afforded by the furan oxygen. Disconnection of two bonds to a common atom, the spiro carbon, in **3** leads to major topological simplification, and suggests a nucleophilic precursor synthon **14** and a biselectrophilic precursor synthon **15**. The eneyne **16** is a synthetic equivalent of **15** that should provide **3** directly because 1,4-addition of a nucleophile will decrease the unsaturation level of each electrophilic center by one unit.



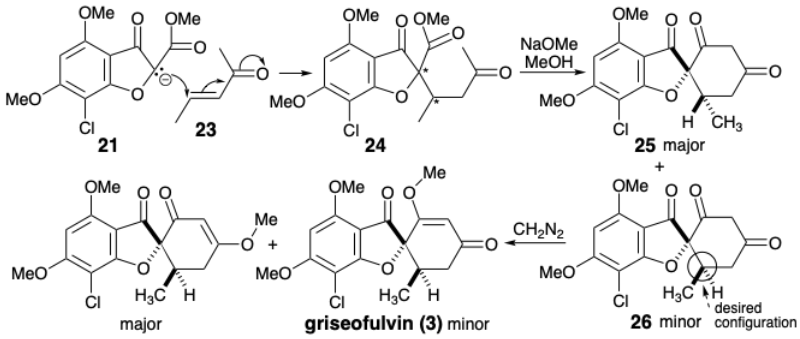
The biselectrophile **16** was prepared from methoxyacetylene and crotonaldehyde, and the precursor **14** of the requisite dissonant nucleophile was obtained from phloroglucinol (**10**) via **18** produced by acylation of **11** with chloroacetyl chloride. It should be noted that the dissonance in the furan ring of **14** is derived from the dissonant precursor chloroacetyl chloride. Treatment of a mixture of **14** and **16** with base delivered **3** via anions **19** and **20**.[3]



A different strategy is also suggested by a polar analysis that ignores the polar activation afforded by the furan oxygen. Disconnection of two bonds of the cyclohexenone ring as in **3** suggests a well precedented annelation of cyclohexanediones that is similar to a Robinson annelation (see section 4.7). In contrast to the previous strategy, a methyl enol ether is not produced directly. The enone **23** serves as synthetic equivalent for the synthon **22**.

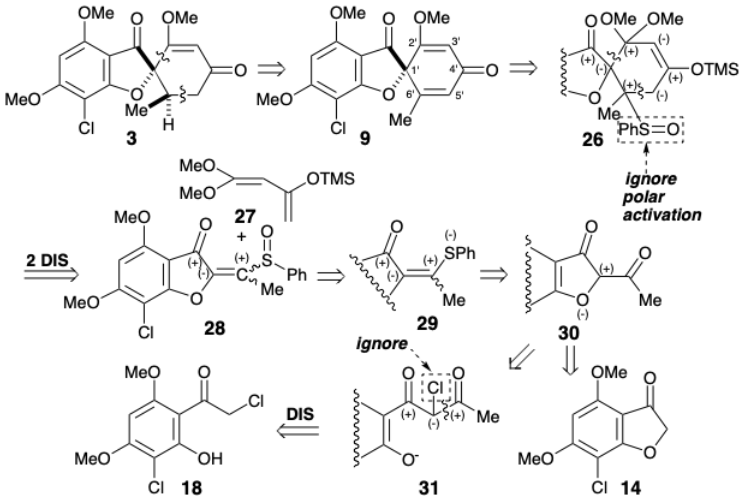


Condensation of **21** with **23** gives two diastereomeric cyclohexanediones **25** and **26**. This synthesis is less efficient than the previous one because the major diastereomer **25** is epimeric with the natural product **3** and methyletherification of the minor diastereomer **26** occurs with unfavorable regioselectivity.[4]

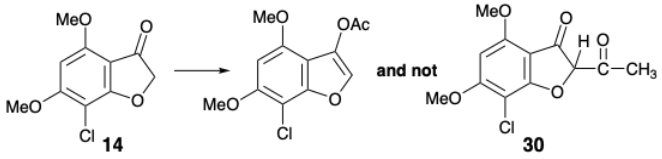


A Cycloaddition Strategy for Griseofulvin

Danishefsky's strategy for a total synthesis of griseofulvin[5] was designed around his method for cyclohexenone annelation through Diels-Alder reaction of highly oxygenated dienes, e.g., **27**.



This *boundary condition* guides and channels the retrosynthetic analysis to seek a two-bond disconnection of the cyclohexenone ring to a butadiene and dienophile precursor. Furthermore, the stereoselective conversion of **9** to give **3** established previously[2] was adopted to simplify the stereochemistry of the target. The dislocation to **9** removes one asymmetric center, that can be introduced at the end of the synthesis by stereoselective hydrogenation. For the desired Diels-Alder *reaction*, a C=C bond between carbons 3' and 4' is required. Therefore, the 2',3' and 5',6' C=C bonds in **9** must be generated after the key Diels-Alder step. The requisite 3',4' C=C bond is provided by dislocation of **9** to the enol-keta1 derivative **26**. The 5',6' C=C bond could be introduced in **26** by a variety of elimination processes. The choice of a sulfoxide as leaving group is dictated by the additional utility of the sulfoxide group for activating the dienophile **28** toward Diels-Alder reaction with the diene **27** which is necessarily electron-rich. The sulfoxide can also be expected not to control the structural selectivity of the Diels-Alder reaction, that will be controlled instead by the carbonyl group of the furanone ring in **28**. The electron withdrawing sulfoxide group is dissonant with respect to the furanone carbonyl in **28**, but it can be obtained by oxidation of the corresponding electron donating sulfide group in **29.** This consonant vinyl sulfide is simply an enol sulfide derivative of the dione precursor **30**. This dione might be available by acylation of the furanone **14** that was used in a previous synthesis of griseofulvin. Alternatively, construction of the dissonant C-O bond in **30** could be achieved after completion of the carbon skeleton but a nucleofuge would be required in **31** because the carbonyl groups can not provide the requisite electrophilicty. Ignoring the chloro group in **31**, the 1,3-dicarbonyl array is consonant and can be constructed by Claisen acylation of the ketone **18** that was also used in the previous stereoselective synthesis discussed above.



In fact, O-acylation of the enolate anion from **14** occurs to the complete exclusion of carbon acylation required to produce **30**. On the other hand, an intramolecular delivery of the acetyl electrophile in **32** served to unmask Intramolecular O-alkylation of the intermediate phenolate **33** delivered the desired dione **30** that exists as an enol tautomer. Conversion of the enol sulfide **29** from **30** into the corresponding sulfoxide was accomploshed by selective oxidation of the sulfide in the presence of a C=C bond with MCPBA at low temperature. Diels-Alder addition of the resulting vinyl sulfoxide **28** to the 1,3-diene **27** was followed, in situ, by thermal elimination of phenylsulfenic acid and methoxytrimethylsilane from an intermediate cyclohexene **26** to deliver cyclohexadienone **9**.