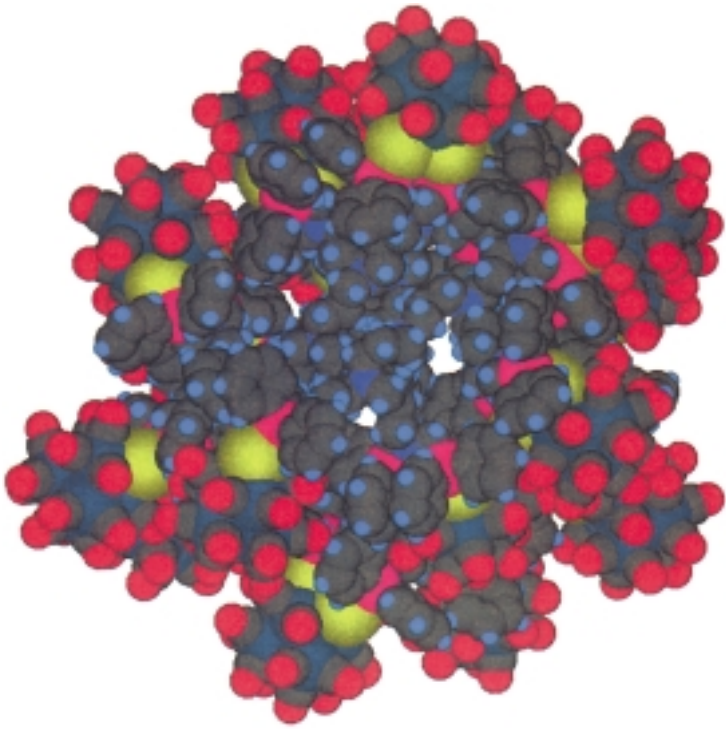

Figure 6. Chem 3D model of **2** (minimized by using modified MM2 parameters and molecular dynamics). Color code: Oxygen (red), hydrogen (light blue), ruthenium (dark green), carbon (black), phosphorus (violet), nitrogen (dark blue), gold (yellow).

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The Synthesis of Streptogramin Antibiotics: (−)-Griseoviridin and Its C-8 Epimer**

Curt A. Dvorak, William D. Schmitz, Daniel J. Poon, David C. Pryde, Jon P. Lawson, Richard A. Amos, and Albert I. Meyers*

The streptogramin antibiotics are a family of compounds that were isolated from a variety of soil organisms belonging to the genus *Streptomyces*.[1] On isolation they can be separated into two distinct groups, one of which is termed Group A containing a 23-membered unsaturated ring such as that found in griseoviridin (**1**),[1] madumycin II (**2**),[2] and virginiamycin M_2 (**3**).[3] Also isolated from this family of mold metabolites are macrocyclic depsipeptides (e.g. etamycin (**4**)[4]), known as Group B, which usually contain five to seven amino acids in a cyclic array (Figure 1). The antibiotics in

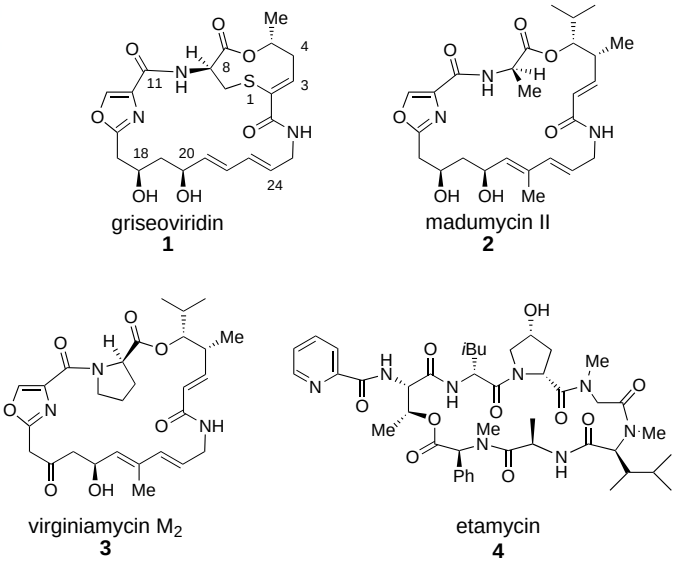

Figure 1. Streptogramin antibiotics.

Group A (**1**–**3**) exhibit a strong synergism when combined with those in Group B with respect to their activity toward Gram-positive bacteria. Recently, the Food and Drug Administration (FDA) (USA) has approved a combination of Group A and Group B to be used against bacteria which have already shown resistance toward vancomycin.[5]

In 1996 we described[2] the synthesis of madumycin II (**2**) and Schlessinger and Li[3] simultaneously reported the total synthesis of virginiamycin M_2 (**3**). Pattenden et al. subsequently reported the synthesis of 14,15-anhydropristinamy-

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cin II_B.[6] The presence of the properly substituted nine-membered ring lactone containing an ene–thio linkage in **1** adds considerably to the complexity of the synthetic problem for reaching griseoviridin (**1**). A number of groups[7] have attempted the synthesis of griseoviridin over the past 20 years and none have met with success until this current report.

The structure of griseoviridin was determined in 1976 by X-ray studies[8, 9] but was reported in error with regard to the relative C-18,C-20 configuration. The correct configuration of the 1,3-diol system in **1** and **2** is *syn* as shown in Figure 1. Here we report the first successful synthesis of (−)-griseoviridin (**1**) as well as its C-8 epimer which were obtained from parallel syntheses starting with D-cystine for griseoviridin and L-cystine for C-8 *epi*-griseoviridin.

The synthetic plan to (−)-**1** hinged on the two crucial fragments, **5**[10] and **6**, which had to be prepared in high enantiomeric purity and then coupled to provide the proper precursor to (−)-**1** (Figure 2). This would require, in a retrosynthetic manner, disconnection of **1** at C-11 (amide bond) and an attempt at an unprecedented olefin metathesis at C-24–C-25, using the diene present in **6**.

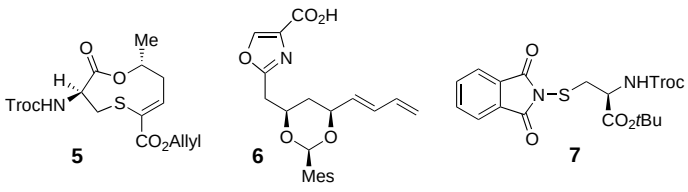
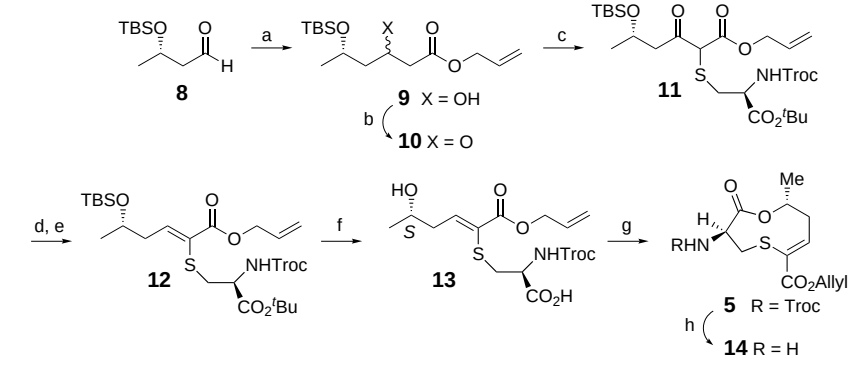


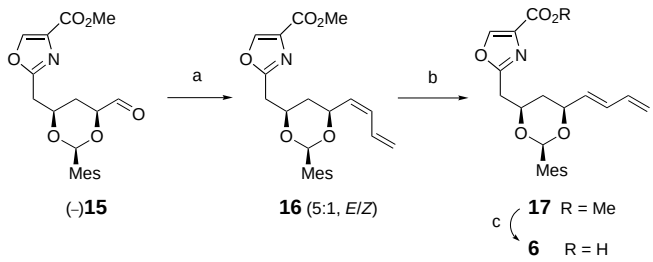
Figure 2. Key coupling fragments for griseoviridin and *S*-phthalimide **7**. Troc = trichloroethoxycarbonyl, Mes = mesityl.

The lactone **5** was assembled in the following manner (Scheme 1). Known aldehyde **8**[11] was treated with the lithium enolate of allyl acetate providing a diastereomeric mixture of β-hydroxy allyl esters **9**, which were directly oxidized with the Dess–Martin reagent[12] to give the β-keto ester **10**. Preparation of the *S*-phthalimido compound **7** (see Figure 2) from commercially available D-cystine was effected by using a procedure adapted from the work of Miller et al.[7e] The key carbon–sulfur bond in **11** was then constructed by treatment of **10** with sodium hydride and *S*-phthalimide **7** in THF. The vinyl sulfide linkage in **12** was then installed by reduction of the β-keto ester **11** with $NaBH_4$ followed by treatment with CH_3SO_2Cl. This resulted in the elimination of the in situ formed mesylate providing the required vinyl sulfide **12** as a 20:1 mixture of olefin isomers (*Z*/*E*). Removal of the secondary TBS silyl ether and the *tert*-butyl ester could be effected simultaneously to give hydroxy acid **13** in good overall yield. Lactonization, under Mitsunobu conditions,[13] proceeded with inversion[14] at the secondary hydroxy groups to give the appropriately substituted ene–thiol lactone **5** in 50–70% yield. Removal of the Troc group[15] by Cd-Pb reduction provided the primary amine **14** to be used in the coupling with the diene oxazole moiety **6**.



Scheme 1. Synthesis of lactone **5**. a) Allyl acetate, LDA, Et_2O, −78 °C, 83%; b) Dess–Martin periodinane, CH_2Cl_2, 78%; c) NaH, THF, 0 °C, then **7**; 86%; d) $NaBH_4$, dioxane:aq pH 7 buffer:*i*PrOH (12:3:1), 83%; e) MsCl, Et_3N, CH_2Cl_2, 96%; f) 10% aq HCl, DME, 65 °C, 74%; g) DIAD, Ph_3P, THF, 50–70%; h) 10% Cd/Pb, 1M NH_4OAc, THF, 96%. TBS = *tert*-butyldimethylsilyl, LDA = lithium diisopropylamide, Ms = mesyl = methanesulfonyl, DME = 1,2-dimethoxyethane, DIAD = diisopropylazodicarboxylate.

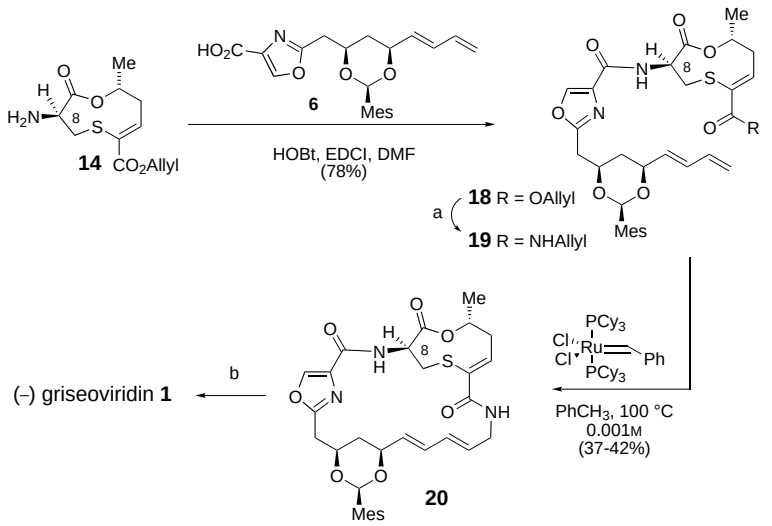
To reach the oxazole-contaning subunit, aldehyde (−)-**15** was prepared from (*S*)-malic acid as previously described[2] (Scheme 2). Wittig olefination of aldehyde **15** with allyl triphenylphosphorane gave the corresponding diene **16** as a mixture of stereoisomers (5:1, *Z*/*E*) in 62% yield. Although the olefination reaction was *Z*-selective, the mixture could be smoothly photoisomerized to the required *E*-diene **17** in the presence of iodine.[16] Removal of the methyl ester in **17** using lithium hydroxide gave the requisite acid **6** to be coupled with lactone **14**.



Scheme 2. Synthesis of oxazole diene **6**. a) Allyltriphenylphosphonium bromide, KHMDS, THF, 62%; b) benzene, I_2, *hv*, 84%; c) LiOH THF/H_2O, 88%. KHMDS = potassium bis(trimethylsilyl) amide.

The amide bond at C-11 was formed from oxazole acid **6** and lactone amine **14** using EDCI and HOBt[17] to afford **18** in good yield. It now became necessary to convert the allyl ester **18** into the allyl amide **19**, since the latter will serve as the properly substituted olefin in the ring-closing metathesis process. To initiate this sequence, the allyl group was removed with $[Pd(Ph_3P)_4]$[18] affording the crude carboxylic acid, and thereafter, coupled with allyl amine (HOBt-EDCI) to afford the cyclization precursor **19** in 82% overall yield (Scheme 3).

The ring-closing metathesis of **19** using 30% Grubbs' catalyst[19] furnished **20** as a single product in 37–42% yield. After a number of additional attempts, the metathesis yield remained within this range. The ^1H NMR spectrum showed no sign of olefin isomers during the metathesis cyclization. Acidic removal of the diol protecting group gave (−)-griseoviridin (**1**) as a single diaster-



Scheme 3. Synthesis of griseoviridin (**1**). a) $[Pd(PPh_3)_4]$, pyrrolidine; allyl amine, HOBt, EDCI, DMF, 82%; b) PPTS, acetone/H_2O, 68%. HOBt = 1-hydroxy-1*H*-benzotriazole, EDCI = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, PPTS = pyridinium-*p*-toluenesulfonate.

eomer in 68% yield. The entire sequence was performed in 24 linear steps from (*S*)-malic acid. The material thus obtained was shown to be identical in all respects to natural griseoviridin[20] (^{1}H, ^{13}C NMR, $[\alpha]_D$, etc.).

The sequence leading to C-8 *epi*-griseoviridin[21] was performed in exactly the same manner and led to a product, in comparable yields, that was distinctly different from natural griseoviridin in its spectroscopic properties. Attempts to ascertain whether ene–thiol lactone **5** could be interconverted to its C-8 epimer proved fruitless due to decomposition when strong bases were employed. Further, attempts to incorporate deuterium into the C-8 position of **5** also failed. In summary, griseoviridin and its C-8 epimer have been synthesized for the first time employing a novel ring-closing metathesis which involved a highly diasteroselective triene to diene macrocyclic ring formation.

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[20] We thank Professor Bycroft for sending us a sample of **1** (over 25 years old) which arrived totally intact, and gave a very clean ^{13}C and ^{1}H NMR spectrum.

[21] A sample of the heretofore unknown C-8 *epi*-griseoviridin has been submitted for antibacterial screening (Aventis) and found to be only very poorly active (courtesy of Dr.S. Dutka-Malen).

A Structural Model for the Galactose Oxidase Active Site which Shows Counteranion-Dependent Phenoxyl Radical Formation by Disproportionation**

Yuichi Shimazaki, Stefan Huth, Akira Odani, and Osamu Yamauchi*

Galactose oxidase (GO) contains one copper ion at its active site and performs a two-electron oxidation of primary alcohols to aldehydes, coupled with a reduction of O_2 to

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