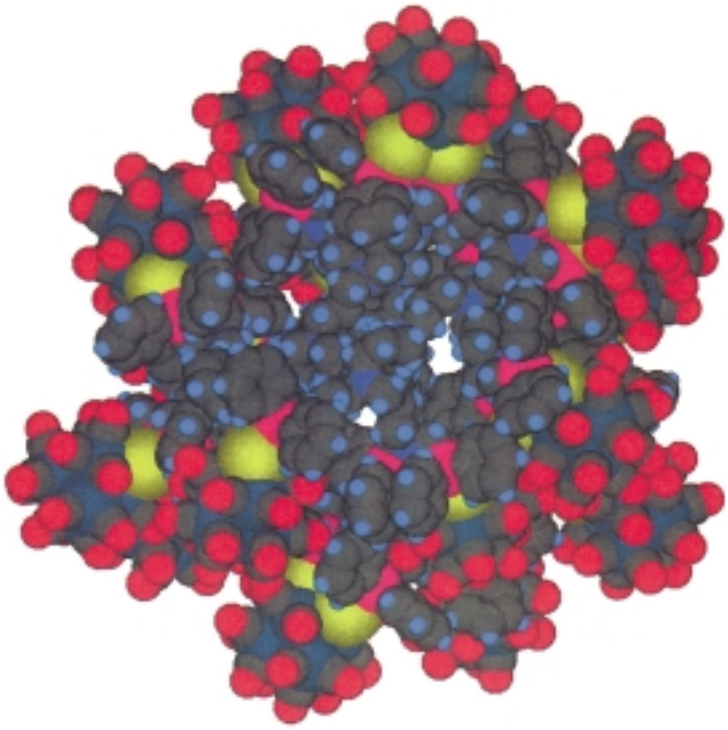

Figure 6. Chem 3D model of **2** (minimized by using modified MM2 parameters and molecular dynamics). Color code: Oxygen (red), hydrogen (light blue), ruthenium (dark green), carbon (black), phosphorus (violet), nitrogen (dark blue), gold (yellow).

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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

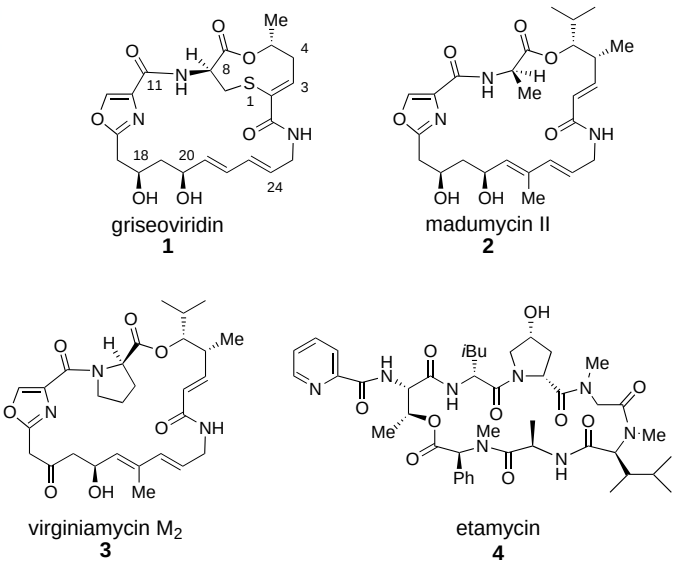

Figure 1. Streptogramin antibiotics.

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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[**] Financial support has been provided by the National Institutes of Health (NIH). We thank the NIH for financial support of this study and Drs. Russell Linderman, Donald Walker, Ronald Spohn, and Enrico Marcantoni for their assistance in various stages of this effort.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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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**.

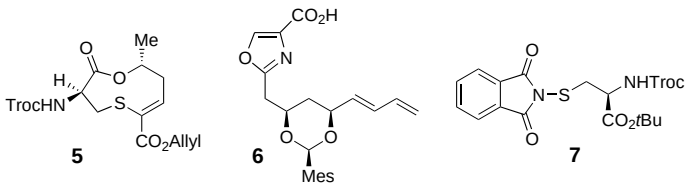
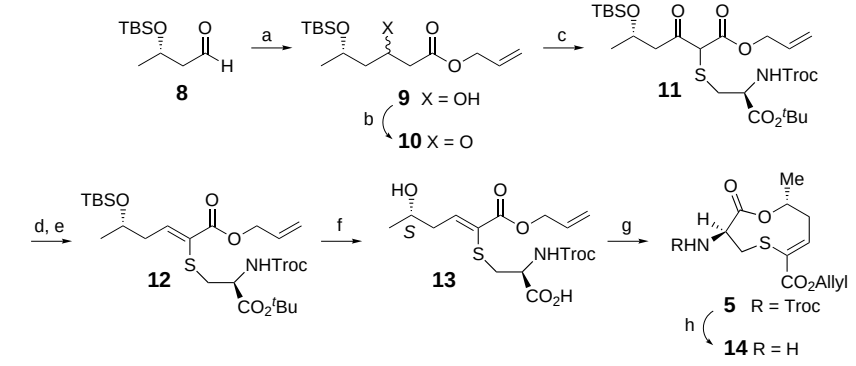


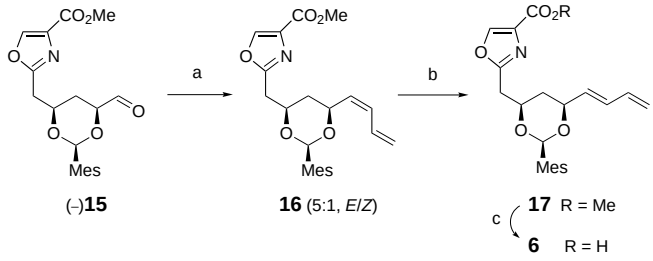
Figure 2. Key coupling fragments for griseoviridin and *S*-phthalimide **7**. Troc = trichloroethoxycarbonyl, Mes = mesityl.

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.

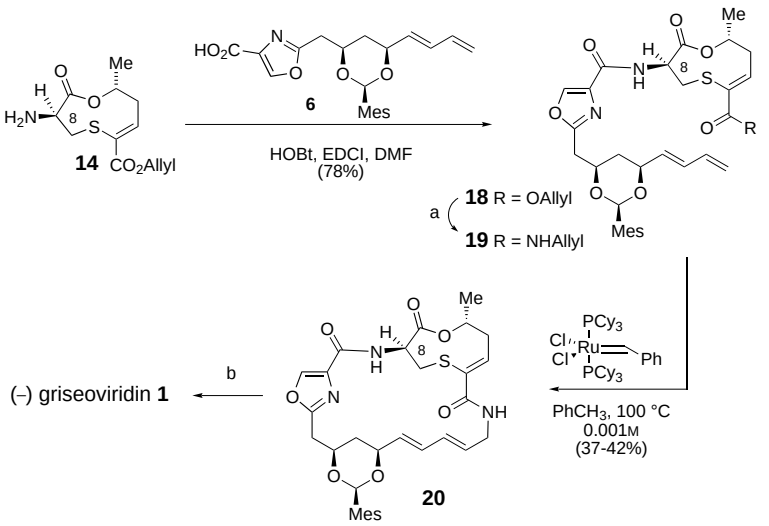
To reach the oxazole-contaning subunit, aldehyde (−)-**15** was prepared from (*S*)-malic acid as previously described[2] (Scheme 2). Wittig olefination of aldehyde **15** with allyl triphenylphosphorane gave the corresponding diene **16** as a mixture of stereoisomers (5:1, *Z*/*E*) in 62% yield. Although 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.

Received: January 3, 2000 [Z14501]

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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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[**] This work was supported by Grants-in-Aid for Scientific Research (No. 09304062 and 0149219 (Priority Areas) to O.Y. and No. 07CE2004(COE) to A.O.) from the Ministry of Education, Science, Sports, and Culture of Japan, for which we express our thanks.

  0570-0833/00/3909-1666 $ 17.50+.50/0