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Stereoselective Synthesis of the C₁₁–N₂₆ Fragment of Griseoviridin

Arun K. Ghosh and Hui Lei

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, USA Fax +1(312)9962183; arunghos@uic.edu

Abstract

The C₁₁–N₂₆ fragment of griseoviridin has been prepared enantioselectively. The 1,3-*syn* diol synthon was derived from lipase-catalyzed selective acylation of (±)-1-(benzyloxy)pent-4-en-2-ol. The conjugated (*E,E*)-dienylmethyl azide functionality was installed by a Pd-catalyzed allylic azidation reaction.

Keywords

alkenes; azides; antibiotics; catalysis; palladium

Griseoviridin (**1**), a member of the streptogramin family of antibiotics, is a broad-spectrum antibiotic produced by a strain of *Streptomyces griseus*.¹ It has exhibited in vitro inhibitory properties against various pathogenic bacteria and fungi. Griseoviridin (**1**) inhibits protein synthesis by interfering with bacterial ribosomal function.² The structure of **1** and its absolute configuration have been determined by X-ray crystallography.³ The unique structural features of griseoviridin (**1**) and its biological properties have attracted much synthetic attention. Retrosynthetically, griseoviridin can be assembled in a convergent manner from two appropriately protected fragments: a C₁₁–N₂₆ dienyl azide fragment **2** and a nine-membered macrocycle **3** (Figure). To date, the only total synthesis of griseoviridin (**1**) has been recently achieved by Meyers.⁴ Several approaches for the synthesis of the oxazole or macrocyclic fragments of **1** have also been published over the years.⁵ Herein we report an enantioselective synthesis of the protected C₁₁–N₂₆ fragment **2** of griseoviridin (**1**) utilizing an optically active 1,3-*syn* diol synthon derived from lipase-catalyzed selective acylation of (±)-1-benzyloxy-pent-4-en-2-ol. A Pd-catalyzed allylic azidation has been utilized to install the conjugated (*E,E*)-dienylmethyl azide functionality selectively.

The synthesis of C₁₁–N₂₆ fragment **2** is illustrated in the Scheme. The known optically active diol **5** was prepared in multigram quantities by enzymatic acylation of (±)-1-benzyloxy-pent-4-en-2-ol as described previously.⁶ Removal of the benzyl group by catalytic hydrogenation of **5** over Pearlman's catalyst provided a triol which was reacted with dimethylbenzylidene acetal in CH₂Cl₂ in the presence of *p*-TsOH at 23 °C to afford benzylidene derivative **6** in 83% yield over 2 steps. Swern oxidation of **6** followed by Wittig olefination of the resulting aldehyde with (triphenylphosphoranylidene)acetaldehyde in benzene at reflux provided a mixture of α, β-unsaturated aldehyde **7** being the major isomer (*E/Z* ratio of 12:1 by ¹H and ¹³C NMR analysis). To install the conjugated primary (*E,E*)-

dienylmethyl azide we have elected to carry out a palladium-catalyzed azidation of the corresponding allyl ester. While Murahashi and co-workers have extensively investigated Pd(0)-catalyzed azidation of allyl esters to primary allyl azides, selective formation of dienylmethyl azides from the corresponding diene acetates has not been examined.⁷ Such conjugated allylamines are structural features of many biologically important natural products.⁸ Thus, treatment of **7** with vinylmagnesium bromide in diethyl ether at 0 °C provided the allylic alcohol which was acetylated with acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP to furnish acetate derivative **8** as a 1:1 mixture in 74% yield for two steps. Exposure of **8** to NaN₃ in a mixture (1:1) of THF and water at 65 °C in the presence of a catalytic amount (5 mol%) of Pd(PPh₃)₄ afforded (*E,E*)-dienylmethyl azide **9** exclusively in 81% isolated yield. The corresponding reaction with Pd(OAc)₂ and PBU₃-derived catalyst was less effective forming azide **9** in only 71% yield. The configuration of the newly formed double bond was confirmed to be *E* by a proton decoupling experiment which showed the coupling constant of the olefinic protons to be 14.7 Hz. To elaborate the oxazole functionality, the isopropyl ester (**9**) was saponified by treatment with aqueous sodium hydroxide in methanol at 23 °C. The resulting acid was coupled with *L*-serine methyl ester in the presence of isobutyl chloroformate and *N*-methylmorpholine to afford amide **10** in 80% yield for two steps. The serine amide **10** was converted to the corresponding oxazoline by treatment with Burgess' salt in THF at reflux for 6 hours.⁹ Subsequent oxidation of the oxazoline with bromotrichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-ene as described by Williams furnished **2** in 62% yield for two steps.¹⁰

In conclusion, an enantioselective synthesis of the C₁₁-N₂₆ fragment of griseoviridin (**1**) has been achieved. Efficient installation of the conjugated (*E,E*)-dienylmethyl azide functionality by a Pd-catalyzed allylic azidation is noteworthy.

All moisture sensitive reactions were carried out under N₂. Anhyd solvents were obtained as follows: THF, distilled from sodium and benzophenone; CH₂Cl₂, distilled from P₂O₅; Et₃N, distilled from CaH₂. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240–400 mesh silica gel under low pressure of 5–10 psi. TLC was carried out with E.Merck silica gel 60-F254 plates. ¹H and ¹³C NMR spectra were recorded on Bruker AM 400 (400 MHz), Avance 400 (400 MHz) and Avance 500 (500 MHz) spectrometers.

(4*S*,6*R*)-6-Isopropoxycarbonylmethyl-4-hydroxymethyl-2-phenyl-1,3-dioxane (6)

To a stirred solution of **5** (804 mg, 2.7 mmol) in EtOAc (30 mL) and MeOH (15 mL) was added Pd(OH)₂ (161 mg). The resulting solution was placed under a H₂ balloon and stirred at 23 °C for 2 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to provide the crude triol (519 mg, 91%), which was used directly for the next step without further purification.

^1H NMR (CDCl_3): δ = 5.01–5.07 (m, 1 H), 4.29 (m, 1 H), 3.98 (m, 1 H), 3.63 (dd, 1 H, J = 3.5, 11.2 Hz), 3.49 (dd, 1 H, J = 6, 11.2 Hz), 3.30 (br, 3 H), 2.45 (d, 2 H, J = 6 Hz), 1.55–1.72 (m, 2 H), 1.24 (d, 6 H, J = 6 Hz).

HRMS (EI): m/z calcd for $\text{C}_9\text{H}_{19}\text{O}_5$ ($\text{M} + \text{H}^+$) 207.1232, found ($\text{M} + \text{H}^+$) 207.1236.

To a stirred solution of the above triol (992 mg, 4.81 mmol) and benzaldehyde dimethyl acetal (1.8 mL, 12 mmol) in CH_2Cl_2 (40 mL) was added *p*-TsOH (46 mg, 0.24 mmol). The resulting mixture was stirred at r.t. for 1 h and was quenched by sat. aq NaHCO_3 . The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 \times 30 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure provided a residue which was purified by column chromatography on silica gel (30% EtOAc in hexanes) to afford the alcohol **6** (1.28 g, 91%); $[\alpha]_{\text{D}}^{23}$ –3.64 (c = 2.75, CHCl_3).

IR (film): 3450, 2979, 2924, 1729, 1106, 1023 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.47–7.50 (m, 2 H), 7.34–7.36 (m, 3 H), 5.59 (s, 1 H), 5.04 (m, 1 H), 4.35 (m, 1 H), 4.03 (m, 1 H), 3.60–3.74 (m, 2 H), 2.70 (dd, 1 H, J = 7, 15.6 Hz), 2.50 (dd, 1 H, J = 6, 15.6 Hz), 2.11 (br, 1 H), 1.51–1.66 (m, 2 H), 1.23 (d, 6 H, J = 6.6 Hz).

^{13}C NMR (100 MHz, CDCl_3): δ = 170.1, 138.0, 128.8, 128.1, 126.1, 100.5, 77.4, 72.9, 68.0, 65.3, 41.2, 31.9, 21.7.

HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{22}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}^+$) 317.1365, found ($\text{M} + \text{Na}^+$) 317.1382.

(4*S*,6*R*)-6-Isopropylloxycarbonylmethyl-2-phenyl-4-[(*E*)-3-oxoprop-1-enyl]-1,3-dioxane (7)

Oxalyl chloride (0.2 mL, 2.2 mmol) was added to CH_2Cl_2 (30 mL) with stirring at -78 °C. The resulting mixture was stirred for 5 min and DMSO (0.3 mL, 4.28 mmol) was added. After 15 min, alcohol **6** (210 mg, 0.71 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 30 min and Et_3N (1 mL, 7.1 mmol) was added. The solution was warmed to 23 °C and quenched with aq sat. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 \times 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to provide the crude aldehyde, which was used directly for next step without further purification. The crude aldehyde and (triphenylphosphoranylidene)-acetaldehyde (216.1 mg, 0.71 mmol) were dissolved in CHCl_3 and heated to reflux for 15 h. The resulting mixture was cooled to r.t. and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc in hexanes) to provide aldehyde **7** (156 mg, 70%); $[\alpha]_{\text{D}}^{23}$ –13.2 (c = 1.0, CHCl_3).

IR (film): 2980, 1728, 1691, 1375, 1147, 1109, 1017 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 9.58, (d, 1 H, J = 8 Hz), 7.49–7.51 (m, 2 H), 7.34–7.38 (m, 3 H), 6.81 (dd, 1 H, J = 4.1, 16 Hz), 6.40 (ddd, 1 H, J = 1.6, 7.9, 16 Hz), 5.67 (s, 1 H), 5.04 (m, 1 H), 4.70 (m, 1 H), 4.40 (m, 1 H), 2.72 (dd, 1 H, J = 7, 15.7 Hz), 2.52 (dd, 1 H, J = 6.4, 15.7 Hz), 1.93 (m, 1 H), 1.60 (m, 1 H), 1.24 (d, 6 H, J = 6.3 Hz).

^{13}C NMR (100 MHz, CDCl_3): δ = 193.3, 169.9, 153.9, 137.6, 131.1, 129.0, 128.3, 120.0, 100.6, 74.8, 73.2, 68.2, 40.9, 35.4, 21.8

HRMS (EI): m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}^+$) 341.1365, found ($\text{M} + \text{Na}^+$) 341.1357.

(4*S*,6*R*)-4-[(1*E*)-3-Acetyloxypenta-1,4-dienyl]-6-isopropoxycarbonylmethyl-2-phenyl-1,3-dioxane (8)

To a stirred solution of aldehyde **7** (156.1 mg, 0.49 mmol) in Et_2O (10 mL) cooled at 0 °C was added a 1 M solution of vinylmagnesium bromide in THF (1 mL, 1 mmol) dropwise. The resulting mixture was stirred at 0 °C for 30 min and was quenched by sat. aq NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to provide the crude alcohol, which was used directly for next step without further purification. To a stirred solution of the above alcohol in CH_2Cl_2 (10 mL) at 0 °C was added Ac_2O (92 μL , 1 mmol), Et_3N (140 μL , 1 mmol) and DMAP (6 mg, 0.05 mmol). The resulting mixture was stirred for 1 h and was quenched by sat. aq NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated and the residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to provide a mixture of acetates **8** as a colorless oil (146 mg, 74% 2 steps).

IR (film): 2961, 1734, 1371, 1234, 1105, 1019 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.48–7.51 (m, 2 H), 7.33–7.35 (m, 3 H), 5.77–5.87 (m, 3 H), 5.73 (m, 1 H), 5.61 (s, 1 H), 5.28 (m, 2 H), 5.04 (m, 1 H), 4.43 (m, 1 H), 4.34 (m, 1 H), 2.69 (dd, 1 H, J = 7, 15.6 Hz), 2.49 (dd, 1 H, J = 6.3, 15.6 Hz), 2.08 (s, 3 H), 1.78–1.83 (m, 1 H), 1.53–1.60 (m, 1 H), 1.24 (d, 6 H, J = 6.3 Hz).

^{13}C NMR (100 MHz, CDCl_3): δ = 170.1, 169.9, 138.2, 134.9, 132.6, 132.5, 128.8, 128.2, 128.0, 127.9, 126.1, 117.6, 100.6, 75.9, 75.8, 74.2, 74.1, 73.2, 68.1, 41.2, 36.4, 21.8, 21.2.

HRMS (EI): m/z calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_6$ ($\text{M} + \text{NH}_4^+$) 406.2230, found ($\text{M} + \text{NH}_4^+$) 406.2235.

(4*S*,6*R*)-4-[(1*E*,3*E*)-5-Azidopenta-1,3-dienyl]-6-isopropoxycarbonylmethyl-2-phenyl-1,3-dioxane (9)

To a stirred solution of acetate **8** (129 mg, 0.33 mmol) in THF (10 mL) and H_2O (4 mL) was added NaN_3 (43 mg, 0.7 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (19 mg, 0.016 mmol). The resulting mixture was heated to reflux for 1 h and cooled to r.t. The layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with

brine, dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (5% EtOAc in hexanes) to provide azide **9** (99 mg, 81%) as a colorless oil; [α]_D²³+0.76 (*c* = 1.3, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ = 7.49–7.51 (m, 2 H), 7.34–7.36 (m, 3 H), 6.24–6.38 (m, 2 H), 5.73–5.86 (m, 2 H), 5.63 (s, 1 H), 5.05 (m, 1 H), 4.46 (m, 1 H), 4.35 (m, 1 H), 3.81 (d, 2 H, *J* = 6.7 Hz), 2.71 (dd, 1 H, *J* = 7, 15.6 Hz), 2.50 (dd, 1 H, *J* = 6.3, 15.6 Hz), 1.80 (m, 1 H), 1.60 (m, 1 H), 1.24 (d, 6 H, *J* = 6.2 Hz).

¹³C NMR (100 MHz, CDCl₃): δ = 170.1, 138.1, 133.8, 133.7, 129.4, 128.7, 128.1, 126.5, 126.1, 100.6, 76.2, 73.1, 67.9, 52.4, 41.1, 36.3, 21.7.

HRMS (EI): *m/z* calcd for C₂₀H₂₅N₃O₄Na (M + Na⁺) 394.1743, found (M + Na⁺) 394.1732.

(1*S*,4*S*,6*R*)-4-[(1*E*,3*E*)-5-Azidopenta-1,3-dienyl]-6-[*N*-(1-hydroxymethyl-2-methoxycarbonyl)acetylamino]-2-phenyl-1,3-dioxane (10**)**

Azide **9** (18 mg, 0.05 mmol) in a mixture of MeOH (3 mL) and 4 N aq NaOH (3 mL) was stirred at r.t. for 12 h. After this period, the mixture was concentrated under reduced pressure. The resulting residue was cooled to 0 °C and acidified to pH 3 with 25% citric acid. The mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to provide the crude acid, which was used directly without further purification. To a solution of the above acid in THF (5 mL) cooled at –30 °C was added *N*-methylmorpholine (17 μL, 0.16 mmol) and isobutyl chloroformate (7 μL, 0.05 mmol). The resulting mixture was stirred at –30 °C for 30 min. *L*-Serine methyl ester (8 mg, 0.05 mmol) was added and the reaction mixture was warmed to 23 °C and stirred for 15 h. After this period, the mixture was evaporated under reduced pressure and purified by column chromatography on silica gel (80% EtOAc in hexanes) to provide amide **10** (17 mg, 80% 2 steps); [α]_D²³+11.5 (*c* = 2.26, CHCl₃).

IR (film): 3367, 2952, 2100, 1744, 1653, 1533, 1217 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.49–7.52 (m, 2 H), 7.35–7.39 (m, 3 H), 6.95 (d, 1 H, *J* = 7.5 Hz), 6.23–6.37 (m, 2 H), 5.71–5.83 (m, 2 H), 5.63 (s, 1 H), 4.65 (m, 1 H), 4.44 (m, 1 H), 4.34 (m, 1 H), 3.79–3.91 (m, 4 H), 3.73 (s, 3 H), 2.51–2.62 (m, 2 H), 1.60–1.80 (m, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 170.7, 170.4, 137.9, 133.7, 133.4, 129.7, 129.1, 128.3, 126.8, 126.2, 100.9, 76.3, 73.6, 63.1, 54.7, 52.7, 52.5, 42.8, 36.2.

HRMS (EI): *m/z* calcd for C₂₁H₂₆N₄O₆Na (M + Na⁺) 453.1750, found (M + Na⁺) 453.1755.

(4*S*,6*R*)-4-[(1*E*,3*E*)-5-Azidopenta-1,3-dienyl]-6-[(4-(methoxycarbonyl)-2-oxazolyl)methyl]-2-phenyl-1,3-dioxane (**2**)

To a stirred solution of the amide (6 mg, 0.01 mmol) in THF (5 mL) was added methyl-*N*-(triethylammoniosulfonyl)carbamate (Burgess' reagent) (6 mg, 0.03 mmol). The resulting mixture was heated to 60 °C for 2 h. After this period, the mixture was cooled to r.t. and passed through a short silica gel column. Evaporation of the solvent under reduced pressure provided the crude oxazoline, which was used directly without further purification. To a stirred solution of the above crude oxazoline in CH₂Cl₂ (3 mL) cooled at 0 °C was added DBU (6 μL, 0.04 mmol) and BrCCl₃ (4 μL, 0.04 mmol). The mixture was warmed to 23 °C and stirred for 15 h. After this period, the mixture was quenched with sat. aq NH₄Cl. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. (3 × 3 mL). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (50% EtOAc in hexanes) to provide oxazole **2** (3.4 mg, 62% 2 steps); [α]_D²³ -6.25 (*c* = 0.48, CHCl₃).

IR (film): 2923, 2102, 1732, 1112 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.19, (s, 1 H), 7.46–7.52 (m, 2 H), 7.31–7.36 (m, 3 H), 6.23–6.37 (m, 2 H), 5.71–5.85 (m, 2 H), 5.62 (s, 1 H), 4.40–4.48 (m, 2 H), 3.92 (s, 3 H), 3.80 (d, 2 H, *J* = 6.4 Hz), 3.24 (dd, 1 H, *J* = 6.5, 15 Hz), 3.08 (dd, 1 H, *J* = 6.5, 15 Hz), 1.78–1.95 (m, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 162.1, 161.5, 144.0, 137.9, 133.6, 133.3, 129.6, 128.8, 128.1, 126.7, 126.1, 125.9, 100.7, 73.9, 52.4, 52.1, 36.2, 34.6, 29.6.

HRMS (EI): *m/z* calcd for C₂₁H₂₂N₄O₅K (M + K⁺) 449.1227, found (M + K⁺) 449.1240.

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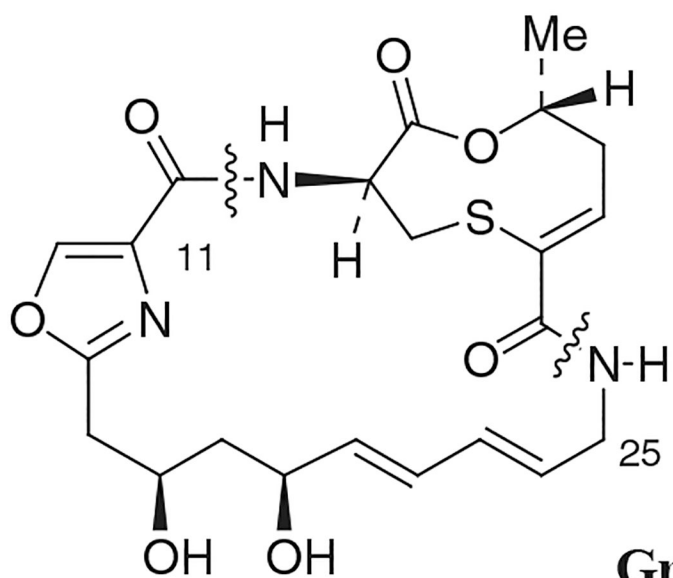
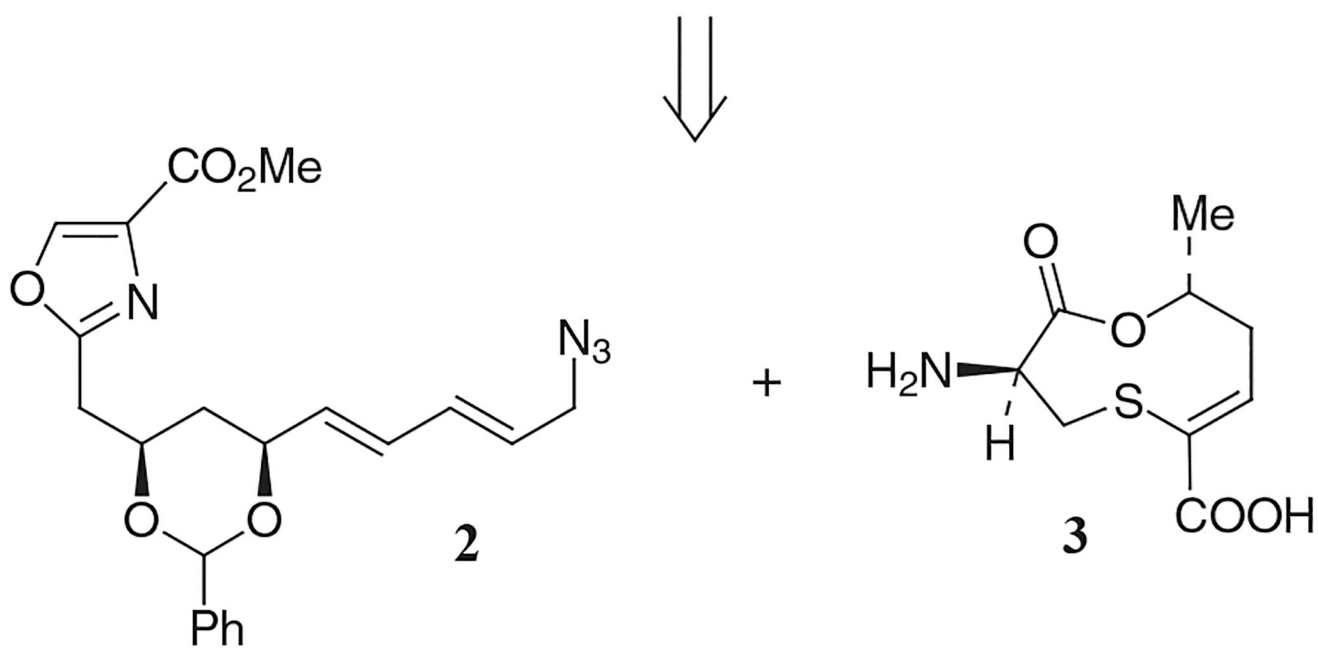
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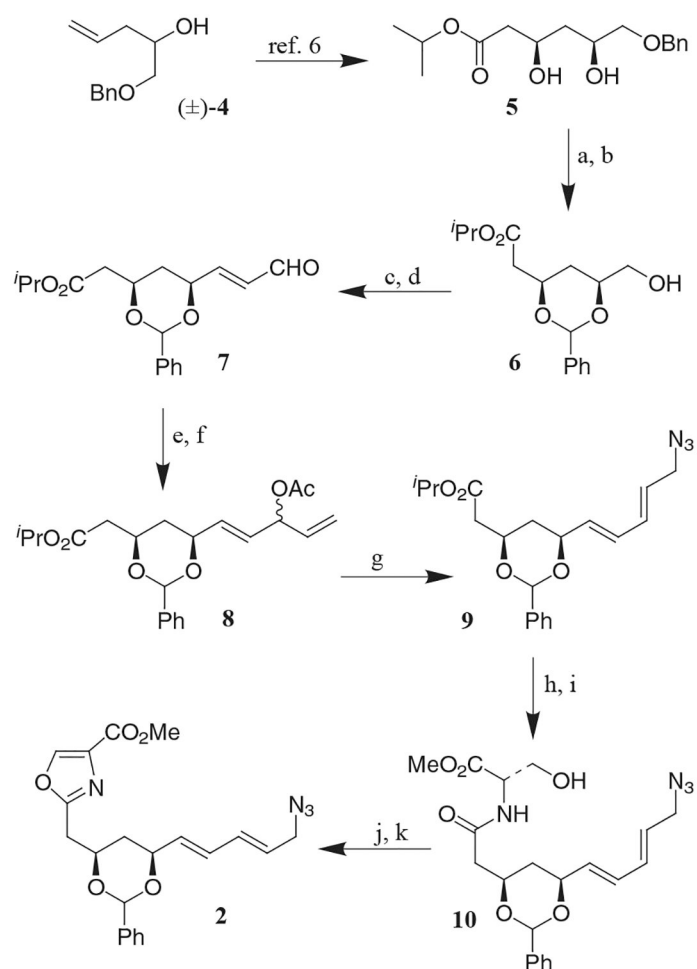
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**Griseoviridin (1)****Figure.**

**Scheme.**

(a) H_2 , $\text{Pd}(\text{OH})_2$, EtOAc , 91%; (b) $\text{PhCH}(\text{OMe})_2$, *p*- TsOH , CH_2Cl_2 , 91%; (c) $(\text{COCl})_2$, DMSO , Et_3N , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; (d) $\text{Ph}_3\text{P}=\text{CHCHO}$, benzene, reflux, 70% for 2 steps; (e) $\text{CH}_2=\text{CHMgBr}$, Et_2O , $0\text{ }^\circ\text{C}$; (f) Ac_2O , Et_3N , DMAP , CH_2Cl_2 , 74% for 2 steps; (g) $\text{Pd}(\text{PPh})_4$, NaN_3 , $\text{THF}-\text{H}_2\text{O}$, $65\text{ }^\circ\text{C}$, 81%; (h) NaOH , $\text{MeOH}-\text{H}_2\text{O}$; (i) *N*-methylmorpholine, isobutyl chloroformate, serine methyl ester \cdot HCl , THF , -30 to $+23\text{ }^\circ\text{C}$, 80% for 2 steps; (j) Burgess salt, THF , reflux; (k) BrCCl_3 , DBU , CH_2Cl_2 , 0 to $23\text{ }^\circ\text{C}$, 62% for 2 steps